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THE CLINICAL USE OF PENICILLIN

OBSERVATIONS IN ONE HUNDRED CASES

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AND
GLADYS L. HOBBY, PH.D.
NEW YORK

Following the announcement of the experimental results of the Oxford workers,[1] studies on penicillin were initiated at the Presbyterian Hospital in the autumn of 1940 and have been carried forward continuously up to the present time. The results of the biologic and chemical phases of the investigation have been reported from time to time elsewhere.[2] In the early stages of the work little attention was paid to the clinical aspects of the problem because of difficulties encountered in producing quantities sufficient for therapeutic purposes and because of the desire to utilize such material as became available for chemical and experimental studies. Enough material was produced, however, to demonstrate that the product was essentially nontoxic for man, and a limited number of patients were treated both locally and systemically.

For preliminary clinical trial, cases of subacute bacterial endocarditis were selected because of the known refractoriness of this disease to other methods of treatment and because many strains of Streptococcus viridans were shown to be susceptible to penicillin "in vitro." It soon became apparent that penicillin, as prepared in our own laboratories, was harmless except for occasional instances of pyrexia and that temporary improvement in the patient's condition with reduction in the number of colonies in the circulating blood could be effected. In no case, however, were the beneficial effects observed other than temporary, and treatment of cases of this disease was therefore abandoned until such time as larger supplies might become available. In the light of subsequent work it became obvious that the amount of penicillin given in this early group of cases was totally insufficient to secure a significant result.

During this stage of the investigation 3 cases of acute pneumococcic endocarditis came under observation. Since it was known that pneumococci were much more sensitive to penicillin than strains of Streptococcus viridans and since all 3 cases proved completely refractory to sulfonamide therapy, they were treated as intensively as possible. In 2 instances there was a dramatic temporary improvement with sterilization of the blood stream for a period, but both patients ultimately succumbed to their infection.

The first of these 2 cases was treated in March 1942. A man aged 53 was apparently recovering uneventfully from a lobar pneumonia (type 7) when he developed a septic temperature. Sulfonamide therapy in adequate dosage failed to improve the situation and a blood culture revealed 650 colonies of pneumococcus (type 7) per cubic centimeter. The patient was given approximately 10,000 units of penicillin every three hours, intravenously. Within twenty-four hours an astonishing improvement in the clinical condition was observed. There was a change from a comatose state to one of mental alertness, the temperature returned to normal and a blood culture taken at the end of the first day was negative. Improvement continued for a further period of forty-eight hours, but the supply of penicillin available was so limited that it was necessary to reduce the dose to 5,000 units every three hours. At the end of seventy-two hours of treatment there was a recurrence of fever, and a blood culture showed 20 colonies per cubic centimeter. The dose of penicillin was again increased to 10,000 units every three hours, and this was followed by a satisfactory improvement in the clinical condition. A negative blood culture was obtained a second time. However, after a further period of forty-eight hours the temperature again rose and successive blood cultures revealed an increasing number of colonies. It became obvious that the infection could not be controlled with the amount of penicillin available, and therapy was therefore discontinued.

In the second case of acute pneumococcic endocarditis, similar results were obtained. After the administration of 30,000 units of penicillin by infusion in the first two hours, followed by 10,000 units every four hours for three doses, a negative blood culture was obtained. A total of 175,000 units was given in the first three days and there was temporary improvement in the patient's condition. It became apparent, however, that the infection could not be controlled with the quantity of penicillin available, and therapy was discontinued.

In spite of the failure of penicillin as employed in these 2 fulminating cases of pneumococcic infection, it was felt that temporary sterilization of the blood stream in both instances represented a considerable achievement.

From these preliminary clinical trials it was apparent that, although penicillin was an extremely powerful bactericidal agent and essentially nontoxic, the amount of material necessary for systemic treatment was far greater than that which was available. A number of

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This paper, in a symposium on "Antibiotic Agents," is published under the auspices of the Section on Experimental Medicine and Therapeutics.

From the Edward Daniels Faulkner Arthritis Clinic of the Presbyterian Hospital and the Department of Medicine, Columbia University College of Physicians and Surgeons.

The clinical material for this study was obtained through the courtesy of the attending staffs of the affiliated units of the Columbia-Presbyterian Hospital Medical Center and other hospitals as well as private physicians.

The penicillin used in the preliminary phases of this study was prepared by Dr. Karl Meyer of the Institute of Ophthalmology, Presbyterian Hospital, from material supplied by Charles F. Pfizer and Company of New York. Since August 1942 all penicillin has been provided by the Committee on Medical Research of the Office of Scientific Research and Development under the supervision of the Committee on Chemotherapeutic and Other Agents, Division of Medical Sciences, National Research Council.

1. Chain, E.; Florey, H. W.; Gardner, A. C.; Heatley, N. G.; Jennings, M. A.; Orr-Ewing, J., and Sanders, A. G.: Penicillin as a Chemotherapeutic Agent, Lancet **2**: 226 (Aug. 24) 1940.

2. Dawson, M. H.; Hobby, Gladys L.; Meyer, Karl, and Chaffee, Eleanor: Penicillin as a Chemotherapeutic Agent, J. Clin. Investigation **20**: 434 (July) 1941. Hobby, Gladys L.; Meyer, Karl, and Chaffee, Eleanor: Activity of Penicillin in Vitro: Observations on the Mechanism of Action of Penicillin; Chemotherapeutic Activity of Pencillin, Proc. Soc. Exper. Biol. & Med. **50**: 277, 281, 285 (June) 1942. Meyer, Karl; Chaffee, Eleanor; Hobby Gladys L.; Dawson, M. H.; Schwenk, Erwin, and Fleischer, G.: On Penicillin, Science **96**: 20 (July 3) 1942. Meyer, Karl; Hobby, Gladys L., and Chaffee, Eleanor: On Esters of Penicillin, ibid. **97**: 205 (Feb. 26) 1943. Hobby, Gladys L.; Meyer, Karl, and Dawson, M. H.: The Nature and Action of Penicillin, J. Bact. **45**: 65 (Jan.) 1943. Meyer, Karl; Hobby, Gladys L., and Dawson, M. H.: The Chemotherapeutic Effect of Esters of Penicillin, Proc. Soc. Exper. Biol. & Med. **53**: 100 (June) 1943. Dawson, Hobby, Meyer and Chaffee.[5]

local infections, particularly staphylococcic infections of the eye,[3] were therefore chosen for topical treatment. Satisfactory results were obtained in several cases and additional evidence gained of the nonirritating nature of the penicillin preparations.

In the meantime the commercial preparation of penicillin under the auspices of the Office of Scientific Research and Development had progressed to the point where material was available for extended clinical trial. Since August 1942 limited quantities have been received through the Committee on Chemotherapeutic and Other Agents of the National Research Council. A general report on the study conducted under the auspices of this committee has recently been published.[4] The present communication is concerned with observations on the treatment of 100 cases which have been under the senior author's personal supervision.

SELECTION OF CASES FOR TREATMENT

Experimental work had clearly demonstrated that penicillin was primarily effective against gram positive organisms, both cocci and rods, and against gram negative cocci. It was further recognized that effective sulfonamide therapy was available for many infections caused by these organisms. Treatment was therefore largely restricted to those infections in which gram positive organisms and gram negative cocci played a dominant role and in which sulfonamide therapy was known to be ineffective. In addition a number of patients who exhibited definite sensitivity to the sulfonamides were treated as well as a few patients with profound anemia or renal insufficiency in whom sulfonamide therapy appeared to be unwise. As a result of these restrictions, staphylococcic infections constitute by far the largest single group in the present study. It should be emphasized, however, that the amount of penicillin necessary to kill staphylococci is considerably greater than that required for other pyogenic cocci. In general, gonococci and meningococci are the most sensitive, followed by pneumococci and hemolytic streptococci. Strains of Streptococcus viridans occupy a position comparable to that of staphylococci. It is therefore apparent that when penicillin becomes generally available its range of usefulness will be greatly extended.

ROUTE OF ADMINISTRATION

For systemic treatment the intramuscular route was chosen in the majority of cases. In the earlier part of the work a number of patients were treated intravenously, but except in very occasional circumstances this route was soon abandoned. It appeared to offer few advantages and several disadvantages. The advantages of the intramuscular route are that (1) a higher concentration is maintained for a longer period of time,[5] although the initial blood level is not so high as that obtained by intravenous administration, (2) the technic of the injections is simpler and can be carried out by a nurse or qualified attendant and (3) the injections are better tolerated by the patient. Occasionally patients complained of the local irritating effect of the intramuscular injection, but the degree of discomfort appeared to be associated with impurities in the product rather than with penicillin itself. With the better preparations the amount of discomfort experienced was minimal.

In instances of general sepsis it may be advisable to administer penicillin by continuous intravenous drip. Further work is required to determine whether the concentrations so achieved are more effective than those obtained by intramuscular injection.

For local treatment penicillin has been administered intrathecally, intrapleurally and intra-articularly. It has also been used for irrigation of sinus tracts and deep wounds and applied as dressings to superficial wounds. Solutions of penicillin have been applied directly to the eye in the form of baths, and relatively high concentrations have been obtained within the eye by iontophoresis.[6] In 1 case of acute laryngotracheitis in an infant, penicillin was instilled directly into a tracheotomy tube at frequent intervals with satisfactory results.

ABSORPTION AND EXCRETION

Our studies on the absorption and excretion of penicillin [5] are in general agreement with those reported by the Oxford workers and in greater detail by Rammelkamp and Keefer [7] and others. These studies show clearly that after intravenous injection penicillin disappears very rapidly from the circulating blood. Within fifteen minutes approximately 75 per cent of the injected material has disappeared and at the end of thirty minutes approximately 90 per cent. The remaining 10 per cent disappears slowly within the next three or four hours. After intramuscular injection the blood concentration rises rapidly, reaching a maximum within fifteen to thirty minutes, remains more or less stationary for the next half hour and then gradually falls off. At the end of three to four hours only traces can be detected in the blood. These observations indicate the advantages of intramuscular administration over intravenous.

After intrathecal administration penicillin has been demonstrated repeatedly in the spinal fluid at the end of twenty-four hours. The same has been shown to be true after both intra-articular and intrapleural administration.

Von Sallmann [8] of the Institute of Ophthalmology of the Presbyterian Hospital has shown that penicillin enters the aqueous humor of the normal eye in small concentrations within thirty-minutes after intramuscular injection. Moderate concentrations are obtained after application of a cup bath to the eye for a period of five minutes, and relatively high concentrations are obtained by iontophoresis. Apparently a different situation exists in the cerebrospinal fluid.[9] In normal persons little or no penicillin is excreted in the cerebrospinal fluid, but in the presence of active inflammation of the meninges detectable amounts may be found.

It should be emphasized that the methods employed in studying the absorption and excretion of penicillin are necessarily rather crude. The selection of a procedure in which the killing power of blood, or other fluid containing penicillin, is determined against a test organism may give information of practical value in estimating the higher levels of drug desirable in

3. These cases were treated by Dr. Philip Thygesson of the Institute of Ophthalmology with material prepared by Dr. Karl Meyer.

4. Keefer, C. S.; Blake, F. G.; Marshall, E. K.; Lockwood, J. S., and Wood, W. B.: Penicillin in the Treatment of Infections, a Report of 500 Cases, J. A. M. A. **122**: 1217 (Aug. 28) 1943.

5. Dawson, M. H.; Hobby, Gladys L.; Meyer, Karl, and Chaffee, Eleanor: Penicillin as a Chemotherapeutic Agent, Ann. Int. Med. **19**: 707 (Nov.) 1943.

6. von Sallmann, Ludwig: Penicillin and Sulfadiazine in the Treatment of Experimental Intraocular Infection with Pneumococcus, Arch. Ophth. **30**: 426 (Oct.) 1943.

7. Rammelkamp, C. H., and Keefer, C. S.: The Absorption, Excretion and Distribution of Penicillin, J. Clin. Investigation **22**: 425 (May) 1943.

8. von Sallmann, Ludwig, and Meyer, Karl: Penetration of Penicillin into the Eye, to be published.

9. Rammelkamp, C. H., and Keefer, C. S.: The Absorption, Excretion and Toxicity of Penicillin Administered by Intrathecal Injection, Am. J. M. Sc. **205**: 342 (March) 1943.

that fluid but give no information regarding the biologic activity of material containing only traces of penicillin. There is reason to believe that this activity is very considerable and of great importance. For example, it can be readily shown that penicillin induces a profound change in the morphology and growth characteristics of hemolytic streptococci in dilutions as high as one part in one billion, far beyond the zone in which either bactericidal or bacteriostatic properties can be demonstrated. Further work is required to determine whether these changes are associated with changes in virulence of the infecting organism and whether they are of clinical significance.

DOSAGE

It was recognized from the beginning of the clinical trials that the establishment of correct dosage and frequency of administration were problems of great complexity. The early experimental work already indicated that different organisms varied greatly in their sensitivity, and more detailed study showed that even different strains of the same organism exhibited wide variations in their susceptibility. In general, strains of gonococcus and meningococcus were found to be most sensitive, followed by pneumococci, hemolytic streptococci (group A), Staphylococcus aureus, Streptococcus viridans, Staphylococcus albus and gram positive rods. Some strains of staphylococci were encountered which were highly resistant. As the work progressed it became the custom to test out the sensitivity of the infecting strain whenever possible. This procedure gives information of great value and is generally recommended, particularly in cases in which a satisfactory response has not been obtained. Details of the method used are being published elsewhere.

Early observations furthermore indicated that another important factor in determining appropriate dosage was the nature of the infection itself. Thus diffuse and phlegmonous lesions as a rule respond much more promptly than localized infections, although the activity of penicillin is not inhibited by pus or other exudates. This may be in large measure due to the actual concentration of the drug which can be attained at a given point. In any event, infections in well vascularized soft tissues respond to concentrations of drug that are apparently completely ineffective in relatively avascular hard tissues such as bone.

It should also be mentioned that little is as yet known concerning the minimal effective concentration for various types of infection. Such experimental work as has been done has been based on the assumption that effective concentrations should be constantly maintained in the circulating blood as is the custom in sulfonamide therapy. Certain facts suggest, however, that this may not always be necessary. Further work is required before any rigid schedule can be formulated, and in cases of doubt it is necessary to rely on the clinical response. In spite of these uncertainties and difficulties the following regimen is tentatively recommended as a result of the experience obtained in treating the present series of cases:

1. *Staphylococcic Infections.*—(*a*) Chronic osteomyelitis and chronic abscess formation, with or without bacteremia (in all such cases, sound surgical procedures should be adhered to and all foreign material, sequestrums and necrotic tissue cleanly removed by radical débridement), 20,000 units every four hours intramuscularly. Duration of treatment is dependent on the severity and extent of the process and on the clinical response.

Local treatment as indicated.

(*b*) Acute osteomyelitis, acute abscess formation, acute phlegmonous cellulitis and so on, 10,000-15,000 units every four hours intramuscularly. Seven days' treatment or less usually sufficient.

(*c*) Minor infections of the genitourinary tract (provided the infecting strain is sensitive), 10,000-15,000 units every four hours intramuscularly. If there is no clinical response in four or five days, continuation of therapy is probably not indicated.

(*d*) Empyema, meningitis or suppurative arthritis, 20,000 units locally daily or every two days for three or four injections. Systemic therapy as indicated by the nature of the primary infection.

2. *Pneumococcic Infections.*—(*a*) Pneumococcic pneumonia, 10,000 units every four hours intramuscularly. Ten injections frequently are sufficient, but continuation of therapy for two or three days may be necessary.

(*b*) Empyema, 20,000 units intrapleurally in 30 or 40 cc. of saline solution every two days for three or four injections. Systemic therapy as indicated.

(*c*) Meningitis, 20,000 units intrathecally daily. Two or three injections usually are sufficient. Systemic therapy as indicated.

3. *Streptococcic Infections.*—(*a*) Infections due to hemolytic streptococci (group A Lancefield), 10,000 units every four hours intramuscularly. Treatment for four or five days is usually adequate except in chronic infections, with or without bone involvement, when prolonged treatment may be necessary.

(*b*) Infections due to hemolytic streptococci other than group A and to Streptococcus viridans (information at present available is insufficient but strains of hemolytic streptococci belonging to groups B, C, D, E, F and G [Lancefield] have been found to be sensitive in vitro; some strains belonging to group D are resistant; strains of nonhemolytic streptococci are, as a rule, from two to four times more resistant than strains of group A hemolytic streptococci), 20,000 units every four hours intramuscularly. Duration of therapy is dependent on clinical response.

4. *Infections Due to Meningococci and Gonococci.*—(*a*) Blood stream infections and acute infections of the genitourinary tract, 10,000-15,000 units every four hours intramuscularly. Two days' therapy is usually adequate. In cases of bacteremia, treatment should be continued for two days after the temperature has returned to normal.

(*b*) Meningitis, 20,000 units intrathecally daily. Two or three injections are usually sufficient. Systemic treatment as indicated.

(*c*) Acute arthritis, 10,000 units intra-articularly daily. Two or three injections are usually sufficient. Systemic therapy if intra-articular therapy is not possible.

5. *Mixed Infections.*—These are usually difficult to treat and relatively resistant. Dosage depends on a variety of factors: 20,000 units every four hours intramuscularly until a clinical response is obtained.

6. *Other Infections.*—Data available are insufficient.

7. *Topical Applications.*—Irrigation of sinus tracts or application of wet dressings daily with solution of penicillin containing 100 units per cubic centimeter are usually satisfactory.

Attention is called to three points in these tentative recommendations: 1. The initial dose recommended is the same as subsequent doses; there seems no valid reason for administering a large initial dose. 2. Higher doses are not recommended in the presence of bacteremia than in cases without bacteremia. In point of fact, the actual sterilization of the blood stream itself is in most instances a comparatively simple matter. 3. Except in general sepsis and for local therapy the intramuscular route is recommended for all injections. It will be apparent from the details of the cases subsequently reported that in many instances the dosage employed was smaller than that recommended in the foregoing schedule, which in itself is somewhat more conservative than that advocated in the recent report of the Committee on Chemotherapeutic and Other Agents.[4] Although the results were satisfactory in the majority of cases, the smaller doses were used in order to conserve the limited supply of penicillin. Probably a more prompt response would have been obtained in certain instances by the use of larger amounts of material. Further experience is required to determine the minimal effective dosage until such time as adequate supplies become generally available.

TABLE 1.—*Cases Treated Systemically*

I. Staphylococcic infections:		
(a) With bacteremia	18	
(b) Without bacteremia	19	
		37
II. Pneumococcic infections:		
(a) Pneumonia	10	
(b) Meningitis	4	
(c) Acute endocarditis	3	
(d) Empyema	2	
		19
III. Streptococcic infections:		
(a) Due to hemolytic streptococci	2	
(b) Due to nonhemolytic streptococci (other than subacute bacterial endocarditis)	2	
(c) Subacute bacterial endocarditis	10	
		14
IV. Meningococcic and gonococcic infections:		
(a) Meningococcic	2	
(b) Gonococcic	8	
		10
V. Mixed infections		14
VI. Infections of questionable causation		6
		100

METHOD OF ADMINISTRATION

Since the intramuscular route appears to be the route of choice except in certain types of infection, and since frequent administration is essential, it is desirable that the drug should be given in as small a volume as possible. The sodium salt is readily soluble in isotonic solution of sodium chloride and can be conveniently administered in amounts of 5,000 units per cubic centimeter. If larger doses are required, the concentration may be increased to 10,000 units per cubic centimeter.

In topical application the Committee on Chemotherapy has recommended solutions containing 250 or 500 units per cubic centimeter. From experimental observations and from our own clinical experience, solutions containing 100 units per cubic centimeter appear to be adequate in the majority of cases. However, no untoward effects have been observed from the use of concentrations far greater than those mentioned, and very possibly better results will be obtained by using stronger solutions.

PENICILLIN RESISTANT STRAINS

As previously mentioned, strains of staphylococci have been encountered which exhibit a high degree of resistance to penicillin. These have invariably been poor pigment producing strains of low virulence. So far, resistant strains of hemolytic streptococci (group A), pneumococci, gonococci or meningococci have not been encountered.

The acquisition of resistance to penicillin by virulent strains of various organisms, especially staphylococci, under both clinical and experimental conditions has been reported by several observers.[10] This is obviously a phenomenon of importance in prolonged therapy and has been advanced as an argument against the use of small dosage of the drug early in treatment. However, its significance seems to be greatly minimized by the further observation that in such instances there was a corresponding loss of virulence of the organism.[11] Furthermore, the acquisition of resistance to the drug must be a relatively rare event, since it was encountered in only 1 possible instance in the present series of cases, many of which were under treatment for prolonged periods.

GENERAL ANALYSIS OF CASES TREATED

Classified according to the nature of the infecting organism, the cases that have been treated systemically are summarized in table 1. No report is made at this time on cases treated topically.

CLINICAL RESULTS

1. *Staphylococcic Infections.*—The staphylococcic infections are divided into two groups, 18 cases with bacteremia and 19 cases without bacteremia, a total of 37 patients (tables 2 and 3).

(*a*) With Bacteremia (18 cases): The ages of the patients with bacteremia varied from 9 days to 74 years; 9 were over 40 years of age. The cases represented a wide variety of conditions, including 5 cases of proved acute osteomyelitis, and infection had persisted for variable periods of time before therapy was instituted. In 2 cases penicillin therapy was used in conjunction with surgical incision and drainage. In 15 of the 18 cases a satisfactory response was obtained; 3 cases relapsed but responded to subsequent therapy, 3 cases terminated fatally and 1 case ended fatally because of a recurrence after an initial response. The 3 cases in which the outcome was fatal deserve special mention: 1. A 9 day infant with pyemia was inadequately treated for four days after the infection had assumed overwhelming proportions. (It will be observed, however, that a completely satisfactory result was obtained in another 18 day old infant with a more or less comparable type of infection which was much more intensively treated.) 2. In a case of epidural abscess and complete paraplegia the local and systemic infection was controlled but death occurred from complications associated with the paraplegia. 3. A patient with acute endocarditis and overwhelming sepsis was treated in the terminal stages of his illness. In the case in which death occurred after an initial response, multiple lung abscesses and bacteremia occurred in a two and a half month infant with cystic fibrosis of the pancreas. The blood stream infection was promptly controlled and the lung lesions gradually healed. Several weeks later, however, the pulmonary infection recurred and, because of difficulties inherent in the nature of the case, further treatment was not instituted. In summary, therefore,

10. McKee, C. M., and Houck, C. L.: Induced Resistance to Penicillin of Cultures of Staphylococci, Pneumococci and Streptococci, Proc. Soc. Exper. Biol. & Med. **53**: 33 (May) 1943. Schmidt, L. H., and Sesler, C. L.: Development of Resistance to Penicillin by Pneumococci, ibid. **52**: 353 (April) 1943.

11. McKee, C. M., and Houck, C. L.: Induced Penicillin Resistance in a Pneumococcus Type III Culture, Federation Proceedings **2**: 100 (March 16) 1943.

satisfactory results were obtained in all cases of staphylococcic bacteremia which could reasonably have been expected to respond. It is realized, of course, that a further follow-up period is required in many instances to determine the ultimate outcome.

Dosage.—The dosage employed in this group of cases varied from 5,000 units every four hours to 25,000 units every three hours. The total amount of penicillin given ranged from 180,000 units (excluding the infant which received only 20,000 units) to 2,250,000 units, and treatment lasted from five to thirty-two days. The wide variations in amounts of drugs administered were in part due to inexperience in the early stages and in part due to the meager supply of penicillin available at different times while the study was under way. Gradually with the accumulation of experience and with a more constant supply of material it became possible to work out a more rational schedule. Further experience is still required, however, before any rigid rules can be laid down, and different clinical conditions almost certainly require different amounts of drug. Examples of probably inadequate treatment are cases 1 and 3. In case 3, in which only 5,000 units was administered every three hours, the infection recurred twice and it was necessary to continue treatment for a total of sixteen days. Case 1, in which 10,000 units was administered every three hours, similarly regressed twice and was treated for a total of thirty days. Very possibly the infection could have been controlled in a shorter period of time had therapy been adequate. On the other hand, the infection in case 6, of desperate illness, in which 25,000 units was administered every three hours for nine days, might very possibly have responded to a smaller amount of drug. Probably the minimal adequate dosage lies somewhere between these two extremes.

From this limited series it is possible to draw the tentative conclusion that acute systemic infections and infections in well vascularized, soft tissues respond more promptly and require a smaller amount of drug than do more chronic infections, especially those in relatively avascular tissue, such as bone. In the former group 10,000 units every four hours would seem to constitute an adequate dose in most instances, while the latter require 20,000 to 25,000 units every four hours. The length of time for which treatment should be continued will vary according to the individual case, but a period of two days after the temperature has become normal would seem to be sufficient in most instances.

Four cases in this group which are of particular interest are briefly summarized:

1. A man aged 49 underwent a reconstruction operation for a probable pathologic fracture of the neck of the femur. The course was uneventful until ten days after operation, when the temperature began to rise. On the twelfth day the patient had a chill with a leukocytosis of 16,000. Inspection of the wound on the fourteenth day showed the presence of purulent material. Blood culture was positive for hemolytic Staphylococcus aureus. Local drainage was instituted and the patient started on sulfadiazine. The wound was opened widely and all sutures were removed. Despite maximal dosage of sulfadiazine and a combination of zinc peroxide and sulfadiazine locally, the patient continued to have elevated temperature with chills for the next four days and the blood culture remained positive. At this time intravenous penicillin 5,000 units every three hours intravenously was started. Forty-eight hours later the blood culture became negative and the temperature came down steadily, returning to normal six days after the beginning of penicillin therapy. Subsequent convalescence was uneventful.

2. A baby aged 18 days, who was said to have had thrush and a postnasal catarrh on discharge from a maternity hospital, was in acute distress on admission, cyanotic, with gasping respirations, and the mouth and nose were full of mucous secretion. A hemorrhagic membrane was present on the posterior pharynx. Nose and throat cultures were positive for hemolytic Staphylococcus aureus without monilias. Blood cultures were also positive for hemolytic Staphylococcus aureus. X-ray exami-

TABLE 2.—*Staphylococcic Infections With Bacteremia*

No.	Clinical Diagnosis	Age	Penicillin: How Treated, Units	Penicillin: Days Treated	Penicillin: Total Dosage, Units	Result	Comment
1	Osteomyelitis	74	10,000 q. 3 h. I. M.	30	2,250,000	Satisfactory	Patient with destruction of L4 and L5; infection recurred twice when therapy was interrupted; final outcome completely satisfactory
2	Osteomyelitis	12	5,000 q. 3 h. I. M.	5	190,000	Satisfactory	Dramatic response in an early acute case
3	Osteomyelitis	15	5,000 q. 3 h. I. M.	16	640,000	Satisfactory	Infection recurred twice; finally cured
4	Osteomyelitis	12	10-20,000 q. 4 h. I. M.	23	1,880,000	Satisfactory	Local infection recurred once when treatment was interrupted
5	Osteomyelitis, suppurative arthritis	12	10,000 q. 3 h. I. V. and I. M., 25,000 intra-articularly in one occasion	19	1,690,000	Satisfactory	Bacteremia and suppurative arthritis controlled; local infection persisted
6	Furuncle	14	5,000 q. 3 h. I. V.	5	180,000	Satisfactory	Blood culture became negative within 24 hours
7	Carbuncle, lung abscesses, pleural effusion	33	25,000 q. 3 h. I. M.	9	1,800,000	Satisfactory	A remarkable recovery in a desperately ill patient; carbuncle drained surgically
8	Perinephric abscess	28	5,000 q. 3 h. I. M.	11	440,000	Satisfactory	Acute infection following surgical drainage; response dramatic
9	Multiple lung abscesses	2½ mo.	2,500 q. 3 h. I. M.	32	602,000	Satisfactory	Infant with cystic fibrosis of pancreas; infection later recurred and patient succumbed
10	Epidural abscess, paraplegia	58	5,000 q. 3 h. I. M.	14	515,000	Died	Systemic and local infection controlled; death due to complications associated with paraplegia
11	Infected surgical wound	49	5,000 q. 3 h. I. V.	6	260,000	Satisfactory	Sulfonamides ineffective
12	Stomatitis, bronchopneumonia, and other conditions	18 days	2,500-5,000 q. 3 h. I. M.	16	495,000	Satisfactory	Sulfonamides ineffective
13	Traumatic urethritis, thrombophlebitis	58	5,000 q. 4 h. I. M.	18	575,000	Satisfactory	Sulfonamides ineffective
14	Pyemia	9 days	500 q. 3 h. I. M.	5	20,000	Died	Infant inadequately treated in terminal stages
15	Bacteremia of unknown origin	56	10,000 q. 3 h. I. M.	10	840,000	Satisfactory	Three positive blood cultures before treatment started; primary infection undetermined
16	Bacteremia of unknown origin, empyema	40	20,000 q. 4 h. I. M.	5	600,000	Satisfactory	Gratifying response in an acutely ill patient; systemic treatment only
17	Acute endocarditis, miliary abscesses and other conditions	73	20,000 q. 4 h. I. M. 1 day; 10,000 q. h. I. V. 2 days	3	480,000	Died	Overwhelming sepsis in a decompensated cardiac with diabetic gangrene
18	Suppurative bursitis	53	20,000 q. 4 h. I. M., local treatment for 10 days	7	600,000	Satisfactory	Severe infection involving entire upper arm treated in combination with surgery

nations revealed diffuse lobular pneumonia. The infant was placed in an oxygen tent and put on atropine and 1 per cent ephedrine nose drops. A 5 per cent solution of sodium sulfadiazine was given subcutaneously. On the sixth hospital day there was no significant improvement in spite of a sulfadiazine blood level of 13 mg. per hundred cubic centimeters. Penicillin was started, 5,000 units every three hours intramuscularly. Within twenty-four hours the baby began to show definite improvement and in succeeding days progress was rapid. The blood culture promptly became negative, the membrane of the mouth entirely disappeared and x-ray examinations during the third week revealed complete clearing of the lobular pneumonia.

3. A boy aged 12 years who had osteomyelitis with hemolytic Staphylococcus aureus septicemia was admitted with chills and fever of four days' duration and pain in the lower end of the femur. Three blood cultures were positive for hemolytic Staphylococcus aureus. Both sulfadiazine and sulfathiazole were administered without apparent effect. Penicillin therapy was instituted, 5,000 units every three hours intramuscularly. The temperature became essentially normal within two and a half days and no growth was obtained in blood cultures. Penicillin was discontinued after five days, and the patient made an uneventful recovery. X-ray examinations of the left femur two weeks later showed thickening of the cortex consistent with early involucrum formation of healing osteomyelitis.

4. A Negro aged 33 years was admitted to the hospital with the history of induration of the lower part of the scrotum for four days and sharp pain in the left lower anterior chest. The chest pain was aggravated by cough and deep respiration. On admission the patient was in acute distress and dyspneic, with a temperature of 104 F., a white blood cell count of 17,000 and pain in the left axillary region. There was a to and fro friction rub over the left lower chest with dulness on the right. The sputum was blood tinged. The perineal portion of the scrotum was swollen, with pus escaping from several sinus tracts. The patient was started on sulfathiazole 6 Gm. a day for two days, then sulfadiazine 6 Gm. a day for two days without response. Blood cultures were positive for hemolytic Staphylococcus aureus, and the clinical condition continued poor. Pleural effusion developed on the left and acute axillary pain on the right with an accompanying friction rub. X-ray examinations of the lungs revealed several areas suggesting early abscess formation. Penicillin therapy was instituted, 25,000 units every three hours intramuscularly. The temperature fell somewhat but remained at levels around 102 F. for five days. A thoracentesis was performed on the third day of penicillin therapy and thin purulent material obtained which grew hemolytic Staphylococcus aureus. The scrotal abscess was incised on the fourth day of penicillin therapy. The temperature continued to drop and reached normal levels on the tenth day, at which time penicillin was discontinued. The lesions in the lungs gradually resolved and the patient was discharged in good condition.

TABLE 3.—*Staphylococcic Infections Without Bacteremia*

			Penicillin				
No.	Clinical Diagnosis	Age	How Treated, Units	Days Treated	Total Dosage, Units	Result	Comment
1	Meningitis	14	5,000 q. 3 h. I. M.	13	500,000	Satisfactory	Meningitis following removal of brain tumor; patient subsequently died with ventricular block; no infection at autopsy
2	Suppurative parotitis	22	5,000 q. 3 h. I. M.	12	490,000	Satisfactory	Critically ill patient with profound anemia, jaundice, hematuria and nitrogen retention following sulfonamide therapy
3	Infected renal cyst	39	5,000 q. 3 h. I. M.	6	280,000	Satisfactory	Patient desperately ill; infected multilocular cyst of kidney ruptured when removed surgically; postoperative course satisfactory
4	Empyema	57	10,000 q. 3 h. I. M., 25,000 q. d. intrapleurally for 4 days	4	305,000	Satisfactory	Gratifying response without thoracotomy
5	Chronic osteomyelitis and suppurative arthritis	56	10,000 q. 3 h. I. M., 10,000 q. d. intra-articularly for 2 days	18	1,400,000	Unsatisfactory	Complicated case in which adequate surgery was not possible; infection temporarily controlled; therapy inadequate for a relatively resistant organism
6	Chronic osteomyelitis	22	10,000 q. 4 h. I. M.	8	400,000	Satisfactory	Adequate surgery
7	Chronic osteomyelitis	23	5,000 q. 3 h. I. M., 10,000 q. d. locally for 12 days	7	300,000	Unsatisfactory	Initial response satisfactory; further treatment with adequate surgery indicated
8	Suppurative arthritis	53	10,000 q. 3 h. I. M., 40,000 q. d. intra-articularly for 5 days	8	830,000	Satisfactory	Dramatic response
9	Furunculosis	69	5,000 q. 3 h. I. M.	3	125,000	Satisfactory	Recurring furunculosis of face and neck; prompt response
10	Furuncle	59	5,000 q. 3 h. I. M.	6	235,000	Satisfactory	Furuncle of nose; gradual response
11	Carbuncle	32	5,000 q. 3 h. I. M.	4	175,000	Satisfactory	Gradual response
12	Deep abscess, secondary to chronic osteomyelitis	52	5,000 q. 3 h. I. M., 2,000 q. 4 h. locally for 10 days	2	130,000	Satisfactory	Recurring abscess in a patient with chronic osteomyelitis; no recurrence in 12 months since treatment
13	Chronic cystitis	43	10,000 q. 6 h. I. M.	12	480,000	Unsatisfactory	Chronic bladder infection of 4 years' duration; etiology not clear
14	Postoperative infection	62	20,000 q. 4 h. I. M.	4	460,000	Satisfactory	Follow-up not obtainable
15	Postoperative infection	12	10,000 in 100 cc. saline q. d. locally	10	100,000	Satisfactory	Infected fascial transplant
16	Scalp infection	42	20,000 q. 4 h. I. M., local treatment for 10 days	2	240,000	Satisfactory	Scalp infection, in a patient with chronic dermatitis, following removal of brain tumor
17	Osteomyelitis	38	10-20,000 q. 4 h. I. M.	11	1,080,000	Satisfactory	Chronic osteomyelitis of 34 years' duration treated in combination with adequate surgery
18	Chronic pyelitis with recurring renal calculi	44	10,000 q. 4 h. I. M.	9	500,000	Unsatisfactory	Organism resistant in vitro
19	Wound infection	50	20,000 q. 4 h. I. M., local treatment for 10 days	2	240,000	Satisfactory	Widespread infection following laminectomy for inoperable cord tumor

(*b*) Without Bacteremia (19 cases): The cases of staphylococcic infection without bacteremia represented an equally heterogeneous group and included 4 cases of chronic osteomyelitis. Satisfactory results were obtained in 15 of the 19 cases. Two of the unsatisfactory results occurred in cases of chronic osteomyelitis in which adequate surgery was not possible. It is of further interest that in 3 of the 4 unsuccessfully treated cases the infecting organism was subsequently found to be resistant to the action of penicillin in vitro. The first of these was a complicated case with avulsion of the foot, suppurative arthritis of the knee and osteomyelitis of the tibia and fibula. Adequate conservative surgery was not possible, and it was ultimately necessary to amputate the extremity. The other cases from which

resistant organisms were cultured were those of chronic pyelitis and chronic cystitis respectively. In the former the infection was associated with recurring renal calculi over a period of years. The urine was temporarily sterilized, but the infection recurred when treatment was discontinued. The remaining case was one of chronic cystitis of four years' duration in which there was some doubt about the precise cause.

Dosage.—The comments with regard to dosage in cases of staphylococcic infection with bacteremia appear to be equally pertinent to cases without bacteremia. In simple soft tissue infections of an acute nature, 10,000 units every four hours would seem to be adequate. In many of the cases in the present series only 5,000 units every three hours was administered. Had larger doses been employed, the period of treatment could probably have been shortened. In chronic infections, especially those involving long bones, the situation is entirely different and much larger doses are indicated, from 20,000 to 25,000 units every three or four hours. Our experience in this type of case is limited, but Major Lyons of the Halloran General Hospital reports [12] that in such infections adequate surgery, with removal of all sequestrums, dead tissue and foreign material is absolutely essential. He recommends a dosage of 20,000 to 25,000 units every three or four hours for two days prior to and for nine days subsequent to complete surgical débridement. He has further found that infections in long bones require larger doses than infections in flat bones.

Brief mention is made of 4 successfully treated cases in this group in which the results were particularly striking:

1. A youth aged 14 years had been operated on for brain tumor and was suffering from meningitis. The postoperative course was stormy, and on the eighth day spinal fluid cultures were positive for hemolytic Staphylococcus aureus. The same organism was recovered on two subsequent occasions. Adequate sulfonamide therapy did not influence the infection. Penicillin was administered, 5,000 units every three hours intramuscularly, and there was a gradual response. Treatment was continued for thirteen days, at the end of which time there was no clinical evidence of infection. The patient subsequently died with a ventricular block and at autopsy no evidence of residual infection was found.

2. A man aged 22 with suppurative parotitis and submaxillary cellulitis had been treated with sulfonamides for a streptococcic sore throat. Three days after the institution of sulfonamide therapy he began to vomit, became jaundiced and passed bloody urine for four days. On admission a large tense area of fluctuation presented in the region of the right parotid gland extending down the neck. The red blood cell count was 1,000,000, hemoglobin was 26 per cent and there was considerable nitrogen retention. The patient was desperately ill, and further sulfonamide therapy was obviously impossible. Surgical drainage, transfusions and penicillin 5,000 units every three hours intramuscularly were instituted. Cultures revealed hemolytic Staphylococcus aureus. A completely satisfactory response was obtained and, although a variety of treatments had been employed, the evidence strongly suggested that penicillin was primarily responsible for controlling the infection. In any event this case clearly demonstrates that penicillin may be safely administered when sulfonamides are contraindicated.

3. A patient with suppurative arthritis of the knee joint following arthrotomy for removal of synovia, medial meniscus and hypertrophic spurs had a normal postoperative course for seven days, when the knee began to be painful. On the ninth day the temperature spiked to 104 F. and the patient had a shaking chill. The knee was found to be grossly infected with hemolytic Staphylococcus aureus. Catheters were placed in the joint, and penicillin was administered both locally and intramuscularly. The patient was given 10,000 units every three hours intramuscularly and 2,500 units locally into catheters every three hours. The improvement was pronounced within twenty-four hours, and the subsequent course was completely satisfactory.

4. A woman aged 57, admitted because of empyema, had a cough of five days' duration and left chest pain. Adequate sulfadiazine treatment produced no response and the temperature continued around 101-103 F. with a white count of 32,000. Signs of fluid appeared over the left lung, and thoracentesis revealed thick pus swarming with hemolytic Staphylococcus aureus. Penicillin was instilled into the pleural cavity, 25,000 units daily for four days together with intramuscular injections of 10,000 units every three hours. At the end of this period the patient was moderately improved, but the temperature continued between 100 and 102 F. and the cultures were still positive, yielding a sparse growth of Staphylococcus aureus. Surgical intervention was contemplated but was withheld in view of the favorable clinical response. In succeeding days the patient continued to improve. The subsequent clinical course was satisfactory without surgical treatment.

2. Pneumococcic Infections.—The pneumococcic infections include 19 cases representing 10 examples of pneumonia, 4 of meningitis, 3 of acute endocarditis and 1 of empyema. In addition, 2 of the pneumonia patients had an infected pleural exudate representing probably an incipient empyema.

(*a*) Pneumonia: The results in pneumococcic pneumonia were satisfactory in all instances except 1, a case of overwhelming sepsis in a parturient female. In this case both the blood stream and the pleural fluid were found to be sterile twelve hours after therapy was started, but the patient died at the end of thirty hours, apparently of toxemia and general collapse. The sterilization of this patient's blood stream and pleural cavity within twelve hours demonstrates the remarkable bactericidal property of penicillin against pneumococci. In the remaining 8 cases the response was dramatic in 4, prompt in 2 and more gradual in the other 2. In general the results were satisfactory with doses of 10,000 units every four hours for one and a half to two days, but in 1 instance there was a dramatic response with a dose of 5,000 units every three hours for one and a half days.

(*b*) Meningitis: The 4 cases of pneumococcic meningitis all responded satisfactorily. In 2 of the 4, however, it was impossible to evaluate the role of penicillin because sulfonamides and antipneumococcus serum also were administered. In the third case the infection persisted in spite of adequate sulfadiazine therapy for twelve days. Penicillin was administered intrathecally, 20,000 units daily for three days, and systemic treatment instituted as well. Within twenty-four hours the temperature returned to normal, the spinal fluid became sterile and thereafter recovery was uneventful. The fourth case was complicated by the presence of mastoiditis and petrositis, and it was necessary to continue treatment for fifteen days before a satisfactory outcome was obtained. In this case also sulfonamides had proved completely ineffective. In 3 of the 4 cases of pneumococcic meningitis, penicillin was administered intrathecally as well as systemically; in 1 case systemic treatment alone was employed. It should be pointed out, however, that in this case the inflammation of the meninges may well have permitted the penicillin to traverse the blood brain barrier, which normally is resistant to its passage.[9]

12. Lyons, Champ: Penicillin Therapy of Surgical Infections in the U. S. Army, J. A. M. A. **123**: 1007 (Dec. 18) 1943.

The 4 cases of meningitis were treated from six to eighteen days, and the total dosage varied from 440,000 to 975,000 units.

(*c*) Acute Endocarditis: Reference has already been made to the 3 patients with acute pneumococcic endocarditis who were treated early in the course of the study. All received what was later recognized as totally inadequate dosage. All three succumbed to the infection, but in 2 instances the blood stream was temporarily sterilized, in 1 case on two occasions. In view of the small amounts of drug employed in such an overwhelming infection, the results at that time were considered encouraging. Since more adequate material has become available, the opportunity to treat such a case has not presented itself.

3. *Streptococcic Infections.*—(*a*) Due to Hemolytic Streptococci (Group A): At the present time there appears to be little indication for the use of penicillin in hemolytic streptococcus infections because of the scarcity of the material and because of the satisfactory response of the majority of such cases to sulfonamide therapy. Cases of sulfonamide intolerance are occasionally encountered and 2 such cases came under observation:

1. A woman aged 55 had suppurative arthritis of the right ankle following compound fracture dislocation. The fibula was plated and the dislocation reduced. Sulfadiazine was given and on the third day after operation the patient developed oliguria and hematuria with a blood urea nitrogen of 76 mg. per hundred cubic centimeters. Sulfonamide therapy was discontinued but was later resumed after a return of kidney function. The first dressing on the thirteenth postoperative day showed that the wound was infected. The leg was put up in plaster, but the fever continued. Sulfonamides were again employed with gradually diminishing urinary output and no clinical improvement. After three months, amputation of the leg was considered. At this time the patient developed classic erysipelas of the face. Penicillin therapy was started, 10,000 units every three hours intramuscularly, and continued for one week. The result was dramatic. Within twenty-four hours the temperature returned to normal and subsequent convalescence was uneventful. At the end of one week the wound looked clean, no cellulitis was present and the area was covered with healthy granulations.

2. A woman aged 43 with a peritonsillar abscess and spreading cellulitis of the pharynx was unable to tolerate sulfonamides because of severe toxic reaction. Penicillin was administered, 10,000 units every three hours intramuscularly. There was satisfactory response and within forty-eight hours the infection had completely subsided.

(*b*) Due to Nonhemolytic Streptococci, not including cases of subacute bacterial endocarditis: Cases of this type of infection are only rarely encountered, and such a bacteriologic diagnosis should be made with care. Two patients were treated, both desperately ill in the terminal stages of their illness. In neither instance was the response satisfactory.

TABLE 4.—*Pneumococcic Infections*

			Penicillin				
No.	Clinical Diagnosis	Age	How Treated, Units	Days Treated	Total Dosage, Units	Result	Comment
1	Lobar pneumonia	40	5,000 q. 3 h. I. M.	3	115,000	Satisfactory	Recovery by lysis; type 25
2	Lobar pneumonia	45	10,000 q. 3 h. I. M.	1½	70,000	Satisfactory	Prompt response; type 7
3	Lobar pneumonia	47	10,000 q. 3 h. I. M.	2	160,000	Satisfactory	Dramatic response within 24 hours; type 7
4	Lobar pneumonia	43	5,000 q. 3 h. I. M.	1½	70,000	Satisfactory	Dramatic response within 12 hours; type 3
5	Lobar pneumonia	49	10-20,000 q. 3 h. I. M.	3	200,000	Satisfactory	Recovery by lysis; type 1
6	Lobar pneumonia	30	10,000 q. 3 h. I. M.	1	100,000	Died	Overwhelming sepsis in a parturient female; blood stream sterilized in 12 hours; death due to general toxemia; type 2
7	Lobar pneumonia	38	10-20,000 q. 4 h. I. M.	1	100,000	Satisfactory	Dramatic response in an apparently sulfonamide resistant case; type 3
8	Lobar pneumonia	22	10-20,000 q. 4 h. I. M.	1½	120,000	Satisfactory	Dramatic response; type 18
9	Incipient empyema following lobar pneumonia	47	20,000 intrapleurally	1	20,000	Questionable	Result difficult to evaluate; type 3
10	Lobar pneumonia, questionable empyema	67	10,000 q. 3 h. I. M., 30,000 intrapleurally	6	480,000	Satisfactory	Oliguria due to sulfonamides; cardiac; type 3
11	Bronchopneumonia	75	5-10,000 q. 3 h. I. M.	5	235,000	Satisfactory	Following prostatectomy; cardiac; type 8
12	Empyema	62	10,000 q. 3 h. I. M., 20,000 intrapleurally on five occasions	3½	375,000	Questionable	Empyema sterilized, thoracotomy to remove exudate; type 1
13	Meningitis, petrositis	37	10,000 q. 3 h. I. M.	15	975,000	Satisfactory	Gradual recovery; sulfonamides ineffective; mastoid drained surgically; type 3
14	Meningitis, mastoiditis	7 mo.	5,000 q. 3 h. I. V. or I. M., 5,000 q. d. intrathecally for 11 days	18	755,000	Recovered	Role of penicillin difficult to evaluate; also received sulfonamides and antipneumococcus serum; mastoid drained surgically; type 6
15	Meningitis, otitis media	5½ mo.	5,000 q. 3 h. I. M. or I. V., 1-5,000 q. d. intrathecally for 6 days	13	440,000	Recovered	Role of penicillin difficult to evaluate; also received sulfonamides and antipneumococcus serum; type 19
16	Meningitis	62	10,000 q. 3 h. I. M., 20,000 q. d. intrathecally for 4 days	6	440,000	Satisfactory	Dramatic response; sulfonamides ineffective; type 6
17	Acute endocarditis *	53	8,000 q. 3 h. I. V.	7	384,000	Died	Blood stream sterilized twice
18	Acute endocarditis *	48	15,000 q. 6 h. I. V.	3½	172,500	Died	Blood stream temporarily sterilized
19	Acute endocarditis,* meningitis	40	?	3	?	Died	An early case; dosage not measured in units

* These 3 cases were among the first cases treated; in the light of subsequent experience, totally inadequate amounts of the drug were given.

(*c*) Subacute Bacterial Endocarditis Due to Nonhemolytic Streptococci: This group of cases represents such a large and important problem that only certain aspects will be touched on in this communication; details will be published elsewhere. When penicillin was first discovered and its remarkable effect on gram positive organisms (including Streptococcus viridans) demonstrated in vitro, high hopes were entertained that it would be successful in combating this almost uniformly fatal type of infection. Despite the limited amount of material which has been available, the results herewith reported would appear in some measure to justify these hopes.

As previously stated, patients with this disease were selected for the preliminary clinical trials of penicillin. When larger amounts of material became available, 5 patients were treated as adequately as the still limited supply permitted. All 5 were classic examples of the disease with rheumatic hearts. In 2 of the 5 patients a satisfactory result was obtained and they are now living and well, thirteen and nine months respectively after treatment was discontinued. The third patient,

whose condition was particularly interesting, responded to penicillin on numerous occasions but invariably the infection recurred within two or three weeks after the discontinuance of treatment. This patient, however, is now in remarkably good general health and it is hoped that it will yet be possible to make a more intensive effort to terminate the infection. Of the 2 patients who were treated unsuccessfully, 1 received only 5,000 to 10,000 units every three hours for three interrupted periods of five days each; the other was intensively sulfonamide therapy.[13] All responded to penicillin and were cured from a clinical and bacteriologic standpoint within forty-eight hours. The dose was 10,000 or 15,000 units every three or four hours for two days.

The cases of arthritis were equally satisfactory. The first was a case of arthritis of the wrist with early destruction of the joint. Sulfonamide therapy and other measures had proved completely ineffective. The response to the administration of penicillin was unequivocal within forty-eight hours, and the final out-

TABLE 5.—*Streptococcic Infections*

No.	Clinical Diagnosis	Age	Penicillin: How Treated, Units	Penicillin: Days Treated	Penicillin: Total Dosage, Units	Result	Comment
			A. Due to Hemolytic Streptococci (Group A)				
1	Avulsion of foot, suppurative arthritis, erysipelas, cirrhosis of liver	55	10,000 q. 3 h. I. M.	8	650,000	Satisfactory	Oliguria and hematuria due to sulfonamides; amputation advised; response to penicillin dramatic
2	Peritonsillar abscess	43	10,000 q. 3 h. I. M.	4	310,000	Satisfactory	Sulfonamide sensitivity
			B. Due to Nonhemolytic Streptococci				
1	Pyemia	30	10,000 q. 3 h. I. M.	12	540,000	Died	Temporary improvement in a desperately ill patient treated in terminal stages
2	Meningitis, petrositis	6	5,000 intrathecally, 10,000 q. 3 h. I. M.	2	200,000	Died	Treated in terminal stages
			C. Subacute Bacterial Endocarditis Due to Nonhemolytic Streptococci				
1-5	Subacute bacterial endocarditis	..	Preliminary clinical trials; dosage very small and not determined in units				No significant results
6	Subacute bacterial endocarditis	23	10-20,000 q. 3 h. I. M.	10	830,000	Recovered	Classic case; rheumatic heart; embolus to right femoral artery
7	Subacute bacterial endocarditis	27	5-10,000 q. 3 h. I. M.	23	1,420,000	Recovered	Classic case; rheumatic heart; embolus to right femoral artery and to left eye
8	Subacute bacterial endocarditis	40	10-40,000 q. 3 h. I. M.	30	6,670,000	Temporary improvement	Blood repeatedly sterilized; patient in excellent clinical condition after 9 months
9	Subacute bacterial endocarditis	28	5-10,000 q. 3 h. I. M.	17	975,000	Died	Temporary improvement only
10	Subacute bacterial endocarditis	23	10-20,000 q. 3 h. I. M.,	33	7,960,000	Died	Blood temporarily sterilized; death due to cerebral embolus; blood culture positive at time of death

TABLE 6.—*Gonococcic and Meningococcic Infections*

No.	Clinical Diagnosis	Age	Penicillin: How Treated, Units	Penicillin: Days Treated	Penicillin: Total Dosage, Units	Result	Comment
			A. Due to Gonococci				
1	Acute arthritis of wrist	42	5,000 q. 3 h. I. M.	6	235,000	Satisfactory	Dramatic response in a sulfonamide resistant case
2	Acute arthritis of knee	41	10,000 q. d. intra-articularly	3	30,000	Satisfactory	Dramatic response with only local treatment
3	Urethritis	25	10,000 q. 3 h. I. M.	2	180,000	Satisfactory	Smears and cultures negative in 2 days
4	Urethritis	24	10-20,000 q. 4 h. I. M.	2	160,000	Satisfactory	Smears and cultures negative in 2 days
5	Urethritis	30	15,000 q. 4 h. I. M.	1½	150,000	Satisfactory	Smears and cultures negative in 2 days
6	Urethritis	23	15,000 q. 4 h. I. M.	1½	150,000	Satisfactory	Smears and cultures negative in 2 days
7	Urethritis	26	15,000 q. 4 h. I. M.	1½	150,000	Satisfactory	Smears and cultures negative in 2 days
8	Urethritis	20	15,000 q. 4 h. I. M.	1½	150,000	Satisfactory	Smears and cultures negative in 2 days
			B. Due to Meningococci				
1	Meningitis	60	10,000 q. 3 h. I. M., 10,000 q. d. intrathecally for 2 days	3	240,000	Satisfactory	Anuria from sulfonamides
2	Meningitis	17 mo.	2,500-5,000 q. 3 h. I. M.	3	77,500	Unsatisfactory	Penicillin not given intrathecally; patient subsequently responded to sulfonamides and antimeningococcus serum

treated but succumbed to a cerebral embolus. At the time of death the blood culture was still positive. Much remains to be learned concerning the most effective method of administering penicillin in cases of subacute bacterial endocarditis, but these preliminary results appear sufficiently encouraging to justify an intensive study of the therapy of this disease as soon as adequate material becomes available.

4. *Gonococcic and Meningococcic Infections.*—(*a*) Infections Due to Gonococci: The number of cases of gonococcic infection treated is limited, but the results have been most instructive and satisfactory. Eight cases in all are reported, 6 of urethritis and 2 of arthritis. The 6 cases of urethritis were completely resistant to

come was a normally functioning joint. The second case of arthritis was treated locally by the injection of 10,000 units daily for three days into the knee joint. The result was dramatic and the patient was discharged on the fifth day, all evidence of infection having subsided.

(*b*) Infections Due to Meningococci: Experience with meningococcic infections has also been very limited and includes only 2 cases. A satisfactory response was obtained in a patient who had developed anuria from sulfonamide therapy. This patient received 10,000

13. Herrell, W. E.; Cook, E. N., and Thompson, Luther: Use of Penicillin in Sulfonamide Resistant Gonorrheal Infections, J. A. M. A. **122**: 289 (May 29) 1943.

units intrathecally on two successive days and 10,000 units every three hours intramuscularly. There seemed to be no doubt that penicillin was responsible for controlling the infection. An unsatisfactory response was obtained in an infant aged 17 months who received only systemic treatment by intramuscular injections. The apparent failure of penicillin in this case lends further support to the finding that this agent does not normally pass through the blood brain barrier. The infection subsequently responded to antimeningococcus serum and sulfonamide therapy.

Four cases which responded satisfactorily in this group are briefly summarized:

1. An infant aged 3 months was acutely ill with laryngotracheitis. A tracheotomy was performed and cultures were positive for hemolytic streptococci, hemolytic Staphylococcus aureus and Streptococcus viridans. Penicillin was administered systemically, 600 units every three hours, and 1 cc. of a solution of penicillin containing 250 units per cubic centimeter was instilled into the tracheotomy tube every three hours. The following day the child seemed better and on the fourth day the temperature was normal. Thereafter recovery was uneventful.

TABLE 7.—*Mixed Infections*

No.	Clinical Diagnosis	Age	Penicillin: How Treated, Units	Penicillin: Days Treated	Penicillin: Total Dosage, Units	Result	Comment
1	Lung abscess	8 mo.	2,000 q. 3 h. I. M.	15	240,000	Satisfactory	Infant with cystic fibrosis of pancreas; blood culture positive for both hemolytic streptococcus and Staphylococcus aureus; remarkable response but infection recurred and infant died
2	Laryngotracheitis	3 mo.	600 q. 3 h. I. M.; 250 q. 3 h. into tracheotomy tube	10	70,000	Satisfactory	Staphylococcus and streptococcus; tracheotomy ineffective
3	Ludwig's angina	60	5,000 q. 3 h. I. M.	7	295,000	Satisfactory	Staphylococcus and streptococcus; aplastic anemia; remarkable response
4	Acute tracheitis, pyemia	34	5-10,000 q. 3 h. I. M.	5	280,000	Died	Staphylococcus and streptococcus; treated in terminal stages
5	Bronchiectasis	56	10,000 q. 3 h. I. M.	3½	280,000	Unsatisfactory	No effect in a chronic case
6	Empyema	62	25,000 q. d. intrapleurally	3	75,000	Died	Putrid empyema; temporarily sterilized
7	Chronic cystitis	62	5,000 q. 6 h. I. M.	6	120,000	Unsatisfactory	Temporary improvement; mixed bacterial flora; anaerobic hemolytic streptococcus predominant
8	Necrotizing ulcer	58	5,000 q. 3 h. I. M., local penicillin dressings	3	120,000	Unsatisfactory	Staphylococcus and streptococcus; organisms resistant in vitro
9	Infected comminuted fracture	36	5,000 q. 3 h. locally by catheter	5	132,000	Satisfactory	Hemolytic Staph. aureus and Neisseriae
10	Lung abscess, metastatic brain abscess	46	10-15,000 q. 3 h. I. M. and I. V.; 20,000 intrapleurally on 8 occasions	50	4,050,000	Satisfactory	Lung abscess cleared; patient ultimately succumbed to brain abscess
11	Osteomyelitis, multiple sinuses, fecal fistula, etc.	57	10,000 q. 3 h. I. M.	8	620,000	Died	A very complicated case
12	Subphrenic abscess, empyema, suppurative pericarditis	29	10,000 q. 3 h. I. M., 50,000 intrapericardially	3	270,000	Died	A very complicated case
13	Cellulitis and multiple abscesses	44	25,000 q. 4 h. I. M., local penicillin dressings q. d. for 8 days	3	560,000	Satisfactory	Definite improvement in general and local condition
14	Necrotizing pharyngitis	7½	10,000 q. 4 h. I. M.	7	420,000	Satisfactory	Necrotizing pharyngitis in a patient with leukemia

TABLE 8.—*Infections of Uncertain Etiology*

No.	Clinical Diagnosis	Age	Penicillin: How Treated, Units	Penicillin: Days Treated	Penicillin: Total Dosage, Units	Result	Comment
1	Atypical pneumonia	56	10,000 q. 3 h. I. M.	4	300,000	Unsatisfactory	No response
2	Atypical pneumonia	23	20,000 q. 3 h. I. M.	3	480,000	Unsatisfactory	No response
3	Atypical pneumonia	48	10-20,000 q. 4 h. I. M.	3	270,000	Unsatisfactory	Questionable response
4	Bronchopneumonia	54	10-20,000 q. 4 h. I. M.	3	270,000	Died	Autopsy not obtained; postmortem cultures of blood, pleural exudate and aspirated lung all negative
5	Bronchopneumonia	4½	10,000 q. 4 h. I. M.	2	100,000	Satisfactory	Etiology obscure
6	Recurring parotitis (von Mikuliez's syndrome)	50	10,000 q. 3 h. I. M.	4	230,000	Unsatisfactory	No response

5. *Mixed Infections* (14 cases).—These cases represent a mixed group both bacteriologically and clinically and are difficult to discuss collectively. The majority were due to mixed infections of staphylococci and streptococci, but in several instances there was a multiplicity of other organisms including gram negative rods. As might have been expected, the results were the least satisfactory of the entire series. Eight of the 14 terminated fatally or gave unsatisfactory results. Almost certainly therapy was inadequate in several instances but, on the other hand, in many cases it seemed doubtful that any type of therapy could have been successful.

2. A patient with aplastic anemia had fulminating Ludwig's angina due to hemolytic streptococci and hemolytic Staphylococcus aureus. The blood count showed only 800,000 red and 400 white cells and no kidney output. Three days of sulfadiazine therapy were without effect. Surgical intervention and tracheotomy were considered too hazardous. Penicillin was administered, 5,000 units every three hours intramuscularly. Within twenty-four hours the condition was definitely improved and within six days the neck had returned essentially to normal. However, the patient continued to pursue a downhill course, presumably because of cerebral bleeding associated with the aplastic anemia. At autopsy a few days later no gross evidence of infection was found in the tissues of the neck.

3. A man aged 36 with a comminuted compound fracture of the lower leg of ten days' duration was given sulfadiazine for four days without effect. Cultures yielded hemolytic Staphylococcus aureus and neisserian organisms. The patient was treated with penicillin locally, the solution being introduced through three catheters. The temperature dropped from levels of 101 and 102 to 99 and 100 F., and the wound became much cleaner. Penicillin was continued for six days, at the end of which time the temperature became normal and the wound continued to remain clean.

4. An infant aged 8 months had a lung abscess with cystic fibrosis of the pancreas. Blood cultures were positive for both hemolytic streptococcus and hemolytic Staphylococcus aureus. Penicillin 2,000 units was administered every three hours intramuscularly for fifteen days. The systemic infection was satisfactorily controlled and the lung lesion gradually disappeared. (Follow-up on this patient two months later showed a recurrence of the pulmonary infection and, in view of the uniformly fatal nature of this disease, further therapy was not employed.)

Only a few brief comments need to be made concerning the unsuccessful outcome in the remaining 8 cases of mixed infection. It has been clearly demonstrated experimentally that penicillin is not effective against gram negative bacilli. Furthermore, the English workers have shown [14] that certain gram negative rods including Escherichia coli actually secrete an enzyme, penicillinase, which destroys penicillin. It is therefore to be expected that the results would be unsatisfactory in cases of mixed infection when organisms of this type are present.

TOXICITY AND REACTIONS

A variety of experimental observations have indicated that penicillin is completely devoid of toxic effects in concentrations far beyond those necessary for therapeutic purposes. These observations have been fully borne out during the clinical trials. It should also be pointed out that the preparations of penicillin at present available are far from pure, the actual amount of pure penicillin being less than one fifth of the injected material. It is therefore possible that such reactions as may be observed may be due to impurities in the preparations or to associated factors attendant on the administration of the drug.

In the present series almost no complications or toxic effects have been observed. Three patients developed a mild urticaria. Chills and fever have not been observed since the early cases when the material was known to contain a pyrogenic substance. Thrombophlebitis, which has been reported by others,[4] has been observed in only 1 instance. This may be due to the fact that in our cases the intravenous route was employed only occasionally. Some patients complained of slight discomfort at the site of the intramuscular injections, but this type of reaction seemed to be connected with particular lots of material. In the great majority of cases no symptoms of any nature were observed.

Prolonged administration has not led to the development of any intolerance or sensitivity. One patient who had been treated intermittently with large doses for more than six months experienced no delayed or cumulative effect of any type. The noteworthy fact has already been commented on that in this case the infecting strain showed no evidence of becoming resistant to the action of penicillin.

SUMMARY AND CONCLUSION

The present clinical study based on 100 cases demonstrates that penicillin is a remarkably effective agent in the treatment of infections due to staphylococci, pneumococci, streptococci, gonococci and meningococci.

The efficacy of penicillin in staphylococcic infections is of importance not because of a special sensitivity of staphylococci but because of the refractoriness of this type of infection to sulfonamide therapy.

A favorable response has been obtained in 15 out of 18 cases of staphylococcic bacteremia; in many instances the effect was dramatic. The 3 cases which terminated fatally all represented problems of great complexity.

The results in 19 cases of staphylococcic infection without bacteremia have been equally impressive. In 3 out of the 4 cases which failed to respond, the infecting organism was subsequently found to be resistant to penicillin in vitro. In chronic osteomyelitis the results have been satisfactory only when penicillin therapy was used in conjunction with adequate surgery. One case of frank empyema and 2 cases with heavily infected pleural exudate have been successfully treated without thoracotomy.

Penicillin has proved highly effective in the treatment of pneumococcic, hemolytic streptococcus, gonococcic and meningococcic infections. In this group 28 cases which failed to respond to sulfonamide therapy or in which sulfonamides were contraindicated have been treated.

TABLE 9.—*Summary of Results*

Type of Infection	No. of Cases	Satisfactory	Questionable	Unsatisfactory
Staphylococcic				
(a) With bacteremia	18	15	..	3*
(b) Without bacteremia	19	16	..	3*
Pneumococcic				
(a) Pneumonia	10	8	1	1*
(b) Meningitis	4	2	2	..
(c) Acute endocarditis	3	..	..	3*
(d) Empyema	2	..	2	..
Streptococcic				
(a) Due to hemolytic streptococci	2	2	..	..
(b) Due to nonhemolytic streptococci (other than subacute bacterial endocarditis)	2	..	..	2
(c) Subacute bacterial endocarditis	10	2	1	7*
Meningococcic and gonococcic				
(a) Meningococcic	2	1	..	1*
(b) Gonococcic	8	8	..	..
Mixed etiology	14	7	..	7
Questionable etiology	6	1	..	5
	100	62	6	32

* See text.

In 9 out of 10 cases of lobar pneumonia, 2 of which showed signs of incipient empyema, the results were uniformly good. The only failure occurred in an overwhelming infection in a parturient female. In this case the blood stream was sterilized within twelve hours, and death apparently resulted from general toxemia. One case of pneumococcic meningitis, which persisted in spite of intensive sulfonamide therapy, yielded promptly to the intrathecal administration of penicillin. The blood stream was temporarily sterilized in 2 cases of acute pneumococcic endocarditis treated with inadequate amounts of material early in the course of the study.

In sulfonamide resistant gonococcic infections, including gonococcic arthritis, the results have been particularly striking.

The response in 1 case of meningococcic meningitis in which penicillin was not administered intrathecally was unsatisfactory.

The results in the treatment of early cases of subacute bacterial endocarditis due to nonhemolytic streptococci have been encouraging.

14. Abraham, E. P., and Chain, E.: An Enzyme from Bacteria Able to Destroy Penicillin, Nature **146**: 837 (Dec. 28) 1940.

In infections of mixed etiology the results have been less uniformly satisfactory. A favorable response has been obtained only in those cases in which gram positive organisms played a dominant role. Penicillin is not effective against gram negative bacilli.

Penicillin has proved ineffective in the treatment of 3 cases of primary atypical pneumonia.

The data at present available indicate that the most practical method of administering penicillin is by intramuscular injection at intervals of four hours. In the presence of severe sepsis intravenous administration may be necessary. Intrapleural and intra-articular administration have been employed with excellent results in cases of empyema and suppurative arthritis. In cases of meningitis, penicillin should be administered intrathecally.

Toxic reactions of a mild nature have been encountered only in occasional instances. Urticaria was observed in 3 cases and phlebothrombosis in 1. These reactions were probably due to impurities in certain preparations and not to penicillin itself.

THE CLINICAL USE OF PENICILLIN

AN ANTIBACTERIAL AGENT OF BIOLOGIC ORIGIN

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At this stage of development of penicillin therapy it is a matter of extreme delicacy to formulate statements which may be considered final with regard to the clinical use of penicillin. It is further true that the treatment of infections with penicillin is accompanied by many problems not as a rule encountered in the use of therapeutic agents heretofore available.

It is well to recall that Fleming [1] in 1929 found that the broth in which Penicillium notatum had grown was inhibitory for certain pathogenic organisms. He named the substance penicillin. Unfortunately, penicillin did not receive clinical application for a period of eleven years following his observations. Penicillin, however, was used in the laboratory during this time for the purpose of isolating unsusceptible organisms. It is proper to award to Fleming the prize of priority for the first attempt to use penicillin in human subjects. He used broth filtrates to irrigate large infected surfaces of man and also irrigated the human conjunctiva every four hours with this material. He reported only that no toxic effects were observed and did not report clinical results.

Following the isolation of an antibacterial agent, gramicidin, from Bacillus brevis by Dubos [2] in 1939, a reinvestigation of substances of biologic origin was naturally undertaken. Chain and other Oxford investigators [3] in 1940 reported on penicillin and its possibilities as a chemotherapeutic agent. One of the first reports on penicillin in America was that by Dawson and his associates [4] at the meeting of the American Society for Clinical Investigation in May 1941. In addition to studies on the antibacterial activity of penicillin, Dawson and his associates mentioned briefly its use in human infections. This report stimulated many investigators to attempt the preparation of penicillin and to study it further. In August 1941 the Oxford investigators [5] further reported on a fairly purified product of penicillin and included in this report the first clinical results. The experimental observations made at the Mayo Clinic on the antibacterial activity of penicillin were presented before the Society of American Bacteriologists in December 1941. Subsequent to this Heilman and I [6] were able to prepare and to obtain small quantities of pencillin for our investigations. In 1942 Heilman, Williams and I [7] reported observations on the clinical effectiveness of penicillin which were in agreement with the results published by the Oxford investigators. The report on penicillin in the treatment of infections published by Keefer and his associates [8] in August 1943 further confirmed the results published by the earlier investigators on the clinical use of this substance.

Penicillin has been used at the Mayo Clinic in the treatment of 62 patients suffering with bacterial infections.[9] A few of the cases have been reported previously; however, our clinical experience to date will be summarized in the present report.

PREPARATIONS OF PENICILLIN SUITABLE FOR CLINICAL USE

Sodium Salt of Penicillin.—Practically all of the experimental and clinical reports which have appeared previously in connection with the work on penicillin have had to do with studies in which the sodium salt of penicillin was used. The sodium salt of penicillin which my associates and I have used in our experimental and clinical studies was that prepared by the Abbott Laboratories. The sodium salt of penicillin is hygroscopic; it is destroyed easily by alterations of the hydrogen ion concentration in the surrounding medium and is sensitive to oxidizing agents. Heat, primary alcohols and metals alter the material. Because of these and other properties, the penicillin must be stored in the ice box at temperatures no higher than 5 C. This material is dispensed usually in sealed ampules and in as nearly the dry state as possible. The sodium salt of penicillin was used in 50 of the 62 cases on which this paper is based.

Calcium Salt of Penicillin.—The Oxford investigators in 1942 and again in 1943 [10] reported their observations on the calcium salt of penicillin. They found

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1. Fleming, Alexander: On the Antibacterial Action of Cultures of a Penicillum, with Special Reference to Their Use in the Isolation of B. Influenzae, Brit. J. Exper. Path. **10**: 226-236 (June) 1929.

2. Dubos, R. J.: Studies on Bactericidal Agent Extracted from a Soil Bacillus: I. Preparation of the Agent; Its Activity in Vitro, J. Exper. Med. **70**: 1-10 (July) 1939.

3. Chain, E.; Florey, H. W.; Gardner, A. D.; Heatley, N. G.; Jennings, M. A.; Orr-Ewing, J., and Sanders, A. G.: Penicillin as a Chemotherapeutic Agent, Lancet **2**: 226-228 (Aug. 24) 1940.

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5. Abraham, E. P.; Chain, E.; Fletcher, C. M.; Gardner, A. D.; Heatley, N. G.; Jennings, M. A., and Florey, H. W.: Further Observations on Penicillin, Lancet **2**: 177-188 (Aug. 16) 1941.

6. Heilman, Dorothy H., and Herrell, W. E.: Comparative Antibacterial Activity of Penicillin and Gramicidin: Tissue Culture Studies, Proc. Staff Meet., Mayo Clin. **17**: 321-327 (May 27) 1942; Comparative Bacteriostatic Activity of Penicillin and Gramicidin, abstr., J. Bact. **43**: 12-13 (Jan.) 1942.

7. Herrell, W. E.; Heilman, Dorothy H., and Williams, H. L.: Clinical Use of Penicillin, Proc. Staff Meet., Mayo Clin. **17**: 609-616 (Dec. 30) 1942.

8. Keefer, C. S.; Blake, F. G.; Marshall, E. K., Jr.; Lockwood, J. S., and Wood, W. B., Jr.: Penicillin in the Treatment of Infections: A Report of 500 Cases, J. A. M. A. **122**: 1217-1224 (Aug. 28) 1943.

9. Herrell, W. E.: Further Observations on the Clinical Use of Penicillin, Proc. Staff Meet., Mayo Clin. **18**: 65-76 (March 10) 1943.

10. Florey, H. W., and Jennings, M. A.: Some Biological Properties of Highly Purified Penicillin, Brit. J. Exper. Path. **23**: 120-123 (June) 1942. Florey, M. E., and Florey, H. W.: General and Local Administration of Penicillin, Lancet **1**: 387-397 (March 27) 1943.

this to be nonhygroscopic and further reported that it could be handled more conveniently than the sodium salt. They made use of it for local therapy. It was their impression, however, that the calcium salt investigated by them was unsafe for intramuscular and intravenous use. Nichols and I[11] recently examined a calcium salt of penicillin (Winthrop) and reported experimental and clinical trials. The potency of this calcium salt investigated by us was 146 Oxford units per milligram and the salt contained 5.6 per cent of calcium. This material had been found by the manufacturer to be quite safe for subcutaneous and intravenous administration to mice.

Using the tissue culture method for the study of cytotoxicity of bactericidal agents which we[12] previously described, Heilman and I found that the calcium salt was somewhat less toxic for cellular elements than the sodium salt of penicillin now commonly used. The decrease of the radius of migration of lymphocytes from lymph node explants as compared with the controls was 13 per cent when the calcium salt was used in concentrations of 1 : 1,000, whereas the decrease of the radius of migration with the same concentration of sodium salt was 27 per cent. Further, the calcium salt appears to be relatively stable. In our laboratories we were unable to detect any loss of activity of the calcium salt in the dry state in sealed ampules which had been stored at room temperature for fifty-six days. The material was kept away from the light. Because of these and other observations, we felt that the calcium salt should prove safe for intravenous and intramuscular therapy. In 12 of the 62 cases included in this report the patients received the calcium salt of penicillin by the intravenous drip method employed at the Mayo Clinic. In order to determine any possible toxic effect from the intramuscular use of the calcium salt of penicillin, the following study was made: To patients not included in this report the calcium salt in amounts of 11,000 Oxford units in 10 cc. of isotonic solution of sodium chloride was administered intramuscularly at three hour intervals. There was no evidence whatever of irritation of tissue.

DOSAGE AND METHODS OF ADMINISTRATION

Local Application.—The sodium and the calcium salt of penicillin as well as the broth filtrates containing penicillin are all satisfactory for local therapy. It appears from the reports now available that the calcium salt is superior to the sodium salt in this form of treatment. The reason is purely a question of stability and ease of handling of the material. The difference in the cytotoxicity of the two preparations is of no significance. Because many antibacterial agents of similar potency are easily available for local therapy, we have not felt justified in using the limited amounts of penicillin available for this purpose. Sulfonamide therapy has proved very satisfactory for the local treatment of bacterial infections. Other agents, such as gramicidin and the synthetic quaternary ammonium compounds, are also very satisfactory. The compounds just mentioned are far more stable than penicillin, and their preparation is not accompanied by the complex problems associated with the production of penicillin. We therefore have used penicillin locally in only 2 cases. The results were satisfactory.

Intramuscular Administration.—No doubt repeated intramuscular injection of penicillin in doses of 10,000 to 20,000 Oxford units dissolved in 5 or 10 cc. of isotonic solution of sodium chloride or distilled water is reliable. Nevertheless this method has some disadvantages. Because penicillin disappears from the blood stream rather rapidly, this method of administration requires repeated injections of the material at three or four hour intervals throughout the entire twenty-four hours. This requires considerable time on the part of medical personnel. Further, if 20,000 units is administered every three hours in this fashion, the total daily dose will be 160,000 Oxford units per patient. This amount of penicillin in our experience is far in excess of that required to obtain satisfactory results in the treatment of infections, including septicemia. Therefore, in order to conserve the limited amount of penicillin available, we have used the intramuscular method of administration in only those cases in which the intravenous drip method was not feasible. Two patients were treated by means of the intramuscular method. One was an infant 10 days of age suffering with staphylococcic septicemia (120 colonies per cubic centimeter of blood). The patient recovered. The second patient was an infant 6 months of age suffering with extensive facial and orbital cellulitis due to Staphylococcus aureus. Suitable veins were not available to permit the use of the intravenous drip administration. The patient recovered.

Intravenous Administration.—Two methods of intravenous administration are possible. Penicillin in concentrated solutions (10,000 Oxford units per 10 cc.) administered every two or three hours has been advocated by some. This results in a daily dose of 80,000 to 120,000 units. This method is subject to the same disadvantages mentioned in the discussion of the interrupted intramuscular method of administration. Larger doses and repeated venipunctures are required, although satisfactory clinical responses may indeed be obtained.

If the interval between the repeated intravenous injections is longer than two hours, it is important to remember that there will be a period during which little or no penicillin is present in the blood. This in my opinion is undesirable, especially in the treatment of infections of the blood stream. In my experience the continuous or nearly continuous intravenous administration of pyrogen free penicillin is the most suitable method. For the treatment of moderately severe or severe infections 40,000 Oxford units per twenty-four hours has been found to be an adequate daily dose of penicillin. Half of the twenty-four hour dose is dissolved in 1 liter of isotonic solution of sodium chloride. The material may be administered in a 5 per cent solution of dextrose in triple distilled water; however, continuous administration of dextrose may produce venous irritation at times. We therefore administer the material in dextrose only in those cases in which the use of sodium chloride is undesirable. Initially, between 100 and 200 cc. of the material is administered at a fairly rapid rate. Following this the rate of injection is regulated to between 30 and 40 drops per minute. The second liter containing penicillin is attached to the

11. Herrell, W. E., and Nichols, D. R.: The Calcium Salt of Penicillin, Proc. Staff Meet., Mayo Clin. **18**: 313-319 (Sept. 8) 1943.
12. Herrell, W. E., and Heilman, Dorothy H.: Tissue Culture Studies on Cytotoxicity of Bactericidal Agents: Effects of Gramicidin, Tyrocidine and Penicillin on Cultures of Mammalian Lymph Node, Am. J. M. Sc. **205**: 157-162 (Feb.) 1943.

continuous intravenous system eight to ten hours later. Repeated venipunctures are avoided by allowing saline or dextrose solution to drip in slowly during the interval in which, for any reason, the subsequent penicillin has not been delivered to the patient's room. An 18 gage Lewisohn transfusion needle is inserted deeply

Fig. 1.—Administration of penicillin by the continuous intravenous drip method with patient recumbent. The patient represented received penicillin in this manner for eight days without withdrawal of the needle. He could move about with the needle in place.

into the vein and anchored with adhesive plaster. A simple arm splint is applied to keep the arm in position. This is tolerated well by the patient and renders this method of administration possible and not uncomfortable. Some patients receiving penicillin in this fashion may be allowed to sit up at times during the course of the therapy. It has been possible to administer penicillin without changing the needle or disturbing the apparatus for a period as long as eight days.

Intrathecal Administration.—Rammelkamp and Keefer [13] made the interesting observation that penicillin could not be detected in the spinal fluid following intravenous administration of the drug to normal subjects. Nichols and I [14] made observations which confirm their findings. We administered as much as 30,000 units of penicillin intravenously in a period of fifteen minutes to a patient who did not have any demonstrable lesions of the central nervous system, and we could not detect any penicillin in the spinal fluid removed thirty and sixty minutes after the intravenous injection. We have not determined whether or not the same finding obtains in diseases which involve the cerebrospinal apparatus, such as meningitis. At the moment, therefore, it seems advisable to supplement intravenous therapy by intrathecal administration of 5,000 to 10,000 Oxford units of penicillin once daily to patients under treatment for meningitis.

Dosage.—Only on two occasions in the treatment of 62 patients have we found it necessary to use more than 40,000 units per day. These two patients received between 40,000 and 60,000 units for one or two days, but in no instance has the daily dose exceeded this amount. It appears that the cases were fairly representative of the moderately severe and severe bacterial infections usually encountered. For example, 16 patients were suffering with septicemia, and the blood cultures of all were positive before treatment.

METHODS OF STANDARDIZING PENICILLIN

The commonly used methods for the standardization of penicillin have been reviewed by Foster and Woodruff.[15] They discussed the principles, the merits and the disadvantages of the different bacteriologic methods now used. They pointed out that the serial dilution methods are wanting in accuracy and advocated a modified broth method devised in their laboratory. The turbidimetric method of Foster used by some is rather difficult for routine purposes. Probably the most commonly used method of assay of penicillin is that described by Abraham and his associates [5] and is known as the Oxford method. The unit is that amount of penicillin which under the conditions of the assay gives an inhibition zone 24 mm. in diameter. The unit also

Fig. 2.—Administration with patient sitting.

may be expressed as that amount of penicillin which regularly inhibits the growth of a known inoculum of the test organism. The test organism used by the Oxford investigators was Staphylococcus aureus.

13. Rammelkamp, C. H., and Keefer, C. S.: The Absorption, Excretion and Distribution of Penicillin, J. Clin. Investigation **22**: 425-437 (May) 1943.

14. Nichols, D. R., and Herrell, W. E.: Unpublished data.

15. Foster, J. W., and Woodruff, H. B.: Microbiological Aspects of Penicillin: I. Methods of Assay, J. Bact. **46**: 187-202 (Aug.) 1943.

Heilman [16] has stated that one of the chief hazards in the methods commonly used is the maintenance of a suitable standard. Using the tissue culture technic, she has devised a method of titrating penicillin which does not require the use of a standard in the performance of the test. This method, which compares favorably with the Oxford method, is the one used in our laboratories for the titration of samples of penicillin. Unless one is interested in some particular problem of a research nature, it is not necessary in my opinion to know the penicillin content of the blood of a patient under treatment. When amounts of penicillin are detectable in the blood by the commonly used methods, the penicillin present is certainly in excess of the ordinary therapeutic requirements. The method described by Heilman is not suitable for the determination of the amounts of penicillin present in the blood and tissues. Her method has been found entirely satisfactory, however, for the determination of the potency of penicillin to be administered therapeutically. Since there is often a discrepancy between the estimated strength of a product at the time of its preparation and the actual strength at the time of its use, one should be prepared to titrate from time to time penicillin to be used clinically. This discrepancy between the estimated and the actual strength of the product is completely understandable in view of the great lability of the product. I am in complete agreement with Heilman that, because of the scarcity of penicillin, it is most important not to use more of it than is necessary. It is likewise most important to use enough. To be able to determine the strength of a preparation of penicillin at the time it is being administered is therefore essential and is the crux of the whole matter.

ANALYSIS OF SIXTY-TWO CASES

Penicillin has been used in the treatment of 62 patients suffering from various bacterial infections. As previously mentioned, in 50 cases the sodium salt and in 12 the calcium salt of penicillin was administered. Penicillin was used locally in only 2 instances. Because of the lack of suitable veins for administration by continuous intravenous drip, penicillin was administered by repeated intramuscular injection in 2 cases. In the remaining 58 cases penicillin was administered by the intravenous drip method previously described. The causative organisms isolated in these 62 cases and the results obtained from penicillin therapy are contained in table 1. The diagnosis in each of the separate groups and the results will be discussed separately.

Staphylococcus Aureus Infections.—In 28 cases Staphylococcus aureus was the organism isolated. Fourteen of the 28 staphylococcic infections were examples of staphylococcic septicemia, in all of which positive blood cultures were obtained before treatment. The results of treatment in the 14 cases of septicemia will be discussed separately. In the remaining 14 cases the blood cultures were negative, but in all but 2 the infections were acute, severe localized staphylococcic infections. The results were entirely satisfactory in 22 of the 28 cases. The result was doubtful in 2, and failure occurred in 4, 2 of which were examples of septicemia associated with clinical evidence of a valvular cardiac lesion at the time the treatment was begun.

16. Heilman, Dorothy H.: Unpublished data.

The clinical diagnoses in these cases were as follows: extensive cellulitis of the face (Ludwig's) or the extremities in 16, infections of the urinary tract in 5, postoperative infection of a wound in 3, osteomyelitis in 2, cellulitis of the thoracic wall in 1 and chronic ulcer in 1.

Injection with Neisseria Gonorrhoeae.—Since the first report from the Mayo Clinic by Cook, Thompson and myself [17] on the experimental and clinical effectiveness of penicillin in the treatment of gonorrheal infection resistant to sulfonamide compounds, further clinical experience indicates that penicillin is highly effective in this condition. Cook, Pool and Herrell [18] have reported the results in detail. Penicillin has been used in a total of 16 cases. In no instance did failure occur. The duration of treatment is seldom more than forty-eight to seventy-two hours. It is never necessary to use more than 100,000 to 150,000 Oxford units of penicillin in these cases. Complete cures have been obtained by using as little as 65,000 units. The intramuscular administration of penicillin is probably quite well adapted to this type of case. On the other hand, we have used the intravenous drip method, which permits a longer period of treatment than is possible with the same amount of penicillin usually necessary for a twenty-four hour course of intramuscular injections. This seems desirable since we continue treatment to the time when the first negative cultures have been reported.

TABLE 1.—*Organism—Results of Treatment with Penicillin in Cases of Acute Localized Infection*

Organism Isolated	Cases	Result		
		Recovery Satisfactory	Doubtful	Failure
Staphylococcus aureus	28	22	2	4
Neisseria gonorrhoeae	16	16	..	..
Streptococci				
Hemolytic	3	2	..	1
Anaerobic	4	4	..	..
Nonhemolytic	3	1	..	2
Actinomyces bovis	4	2	..	2
Micrococcus	2	..	1	1
No organism	2	1	..	1
Total	62	48	3*	11*

* Five of the eleven results listed as failures and one of those listed as doubtful occurred in cases of acute or subacute bacterial endocarditis.

Streptococcic Infections.—Because of the effectiveness of the sulfonamide compounds against hemolytic streptococcic infections, we did not find it necessary to use penicillin in more than 3 cases of this type. In the first instance the diagnosis was multiple hepatic abscesses; the result was unsatisfactory. In the second the diagnosis was extensive cellulitis of the face (Ludwig's) without bacteremia, and in the third the diagnosis was extensive cellulitis of the face with septicemia. Both the patients with cellulitis recovered.

A partially or completely anaerobic streptococcus was isolated in 4 cases. Three of the patients were suffering with osteomyelitis. One had postoperative septi-

17. Herrell, W. E.; Cook, E. N., and Thompson, Luther: Use of Penicillin in Sulfonamide Resistant Gonorrheal Infections, J. A. M. A. **122:** 289-292 (May 29) 1943.

18. Cook, E. N.; Pool, T. L., and Herrell, W. E.: Further Observations on Penicillin in Sulfonamide Resistant Gonorrhea, Proc. Staff Meet., Mayo Clin. **18:** 433-437 (Nov. 17) 1943.

cemia. Satisfactory results were obtained in all 4 instances.

There were 3 cases in which a nonhemolytic streptococcus was the organism isolated. In 2 instances the diagnosis was subacute bacterial endocarditis. In both of these the treatment resulted in failure. In 1 instance the diagnosis was extensive cellulitis of the mouth and tongue; the patient recovered.

Miscellaneous Infections.—In 4 cases actinomycosis was treated with penicillin. In 1 instance the infection was abdominal actinomycosis complicated by carcinoma of the colon; the result was unsatisfactory. In 3 instances the diagnosis was maxillofacial actinomycosis. There were one failure and two recoveries.

In 2 cases a micrococcus was isolated repeatedly from the blood on culture, and both patients were suffering with subacute bacterial endocarditis. The treatment with penicillin was ineffective in 1 patient. The other patient is still living and in spite of the presence of endocarditis the blood cultures are negative. The result is listed as doubtful.

In 1 case an overwhelming gas gangrene infection was present. The patient died before bacteriologic studies could be made and before completion of intravenous administration of 1 liter of saline solution containing 20,000 units of penicillin.

TABLE 2.—*Results of Penicillin Therapy in Cases of Septicemia*

Organism Isolated	Cases	Recovery	Failure
Staphylococcus aureus	14	12	2
Hemolytic streptococcus	1	1	—
Anaerobic streptococcus	1	1	—
Total	16	14 (88%)	2 (12%)

In another case in this series positive bacteriologic results could not be obtained before penicillin was administered. However, the patient was suffering with extensive cellulitis of the face and mouth (Ludwig's). The patient received 240,000 units of penicillin by the intravenous drip method over a nine day period. This patient recovered.

The Question of Surgical Drainage.—On excluding the 16 cases of gonorrhea in which treatment with penicillin was given because the infection was resistant to sulfonamide compounds, there remain 46 instances of infection caused by other pathogenic bacteria. In some of these 46 cases, the infection localized and was susceptible of drainage; however, in only 10 such cases was drainage instituted. Even some of these 10 patients, I believe, would have recovered without drainage.

PENICILLIN IN THE TREATMENT OF BACTEREMIA

Since bacteremia or septicemia constitutes a most serious problem in the treatment of infections, it is appropriate to analyze thoroughly the results that followed the use of penicillin in these cases. In nearly every instance one or more of the sulfonamide preparations had been administered without demonstrable benefit. Included in this group were all the patients whose blood cultures were positive before or at the time of institution of penicillin therapy. The blood cultures in 20 of the 62 cases included in this report were positive.

Four of these cases were examples of subacute bacterial endocarditis, and in spite of temporary sterilization of the blood stream following the administration of penicillin we cannot report at this time a single recovery. These 4 cases are therefore excluded henceforth in the discussion of the results in bacteremia.

In 14 of the 16 cases of septicemia (table 2) the organism isolated from the blood was Staphylococcus aureus. Hemolytic streptococci were isolated in one and anaerobic streptococci in another. Fourteen of the 16 patients suffering with septicemia recovered; 2 died. It is significant that the 2 patients who failed to recover had definite clinical evidence of a possible valvular cardiac lesion at the time penicillin therapy was instituted.

One of these patients was a woman aged 31 who was admitted after having been under treatment with sulfonamide therapy for eighteen days because of staphylococcic septicemia which apparently started from an abscess in the hand. At the time of her admission her blood cultures were negative, and penicillin was not administered. Several days after admission she was delivered of a normal but premature child. At the time of her admission a definite cardiac murmur was present and there were other physical manifestations suggestive of acute endocarditis. At the onset of labor a highly septic fever developed, and blood cultures revealed forty-five colonies of Staphylococcus aureus per cubic centimeter. Subsequent to this penicillin therapy was instituted, but the patient failed to respond favorably and died after three days of treatment. Necropsy revealed acute mitral bacterial endocarditis with multiple abscesses throughout most of the viscera.

The second patient who failed to recover was a man aged 64 under observation for a severe infection of the urinary tract due to Staphylococcus aureus. A positive blood culture for Staphylococcus aureus was obtained on the fourth day after his admission. On the fifth day penicillin therapy was started. At the time penicillin therapy was begun a definite systolic murmur could be heard, and a diagnosis of possible acute endocarditis was made. After receiving 30,000 units of penicillin by the intravenous drip method, the patient died. He had been treated for only a little more than twelve hours. Necropsy revealed acute vegetative endocarditis and multiple abscesses in both kidneys.

It seems likely that both of these patients were suffering with acute vegetative endocarditis at the time penicillin therapy was initiated. In our experience vegetative endocarditis has not developed during treatment with penicillin. Although this group of cases of septicemia is small, it is gratifying to experience recovery of 14 of 16 patients suffering with such a severe infection (recovery rate 88 per cent).

The daily dose of penicillin administered in these cases has been, as a rule, between 30,000 and 40,000 units in twenty-four hours. In the cases of septicemia the total amount of penicillin administered by the intravenous drip method varied between a minimum of 160,000 units and a maximum of 473,000 units. The average duration of treatment of the patients suffering from septicemia was ten and a half days. It is our practice to continue the administration of penicillin until two successive negative blood cultures have been obtained and the temperature has reached normal.

The age of the patient does not appear to be of any prognostic significance under adequate penicillin therapy. The youngest patient treated for septicemia was a child 10 days of age. The oldest patient was 75 years of age. It seems reasonable to assume that satisfactory results can be obtained by using the daily dosage recom-

mended and administering the material by the intravenous drip method. This permits penicillin to be delivered into the blood stream continuously or nearly so, a very desirable factor in the treatment of patients with bacterial infections, especially those whose blood cultures are positive. The average total amount of penicillin used per patient for severe infections is slightly less than 300,000 units. It seems unnecessary to use more if satisfactory results can be obtained with this amount administered by the method advocated.

TOXIC REACTIONS

Chills and Fever.—Chills and fever have been reported by other investigators. All of the material used in our work has been pyrogen free penicillin. In no instance have we observed this reaction.

Thrombophlebitis.—We observed a mild venous irritation in 3 of the 62 cases reported. In all 3 instances this reaction promptly subsided after the intravenous drip had been changed to another site. It is interesting that this occurred only in cases in which penicillin was being administered in a 5 per cent solution of dextrose. Prolonged administration of dextrose itself may result in irritation of veins in some instances. Stronger solutions of penicillin than we have used may be responsible for some of the phlebitis reported to result from penicillin therapy. It is quite possible also that substances introduced in the processing of penicillin, if still present in the final product, may explain this reaction. I am not prepared to state with certainty that the possibilities just mentioned are the true factors involved in "penicillin phlebitis." Certainly the reaction has not been at all troublesome in our experience.

SUMMARY AND CONCLUSIONS

It is apparent that penicillin is a highly effective antibacterial agent against susceptible pathogens. Among the cases in which penicillin was used were infections due to Staphylococcus aureus, Neisseria gonorrhoeae, streptococci, actinomycetes and micrococci. Satisfactory results were obtained in 48 of the 62 cases. The results were doubtful in 3, and failure or death occurred in 11 instances, in 5 of which the condition was acute or subacute bacterial endocarditis. If the latter 5 cases are excluded, the cases in which the results were satisfactory would number 48 of 57 (84 per cent).

Both the sodium and the calcium salt of penicillin have been used in the treatment of the bacterial infections reported. Either of these salts may be applied locally or administered intravenously or intramuscularly. The calcium salt appears to be the more stable.

The experience in this group of cases seems to justify the conclusion that 40,000 units of penicillin per day is sufficient in the treatment of the infections described. In our hands the intravenous drip method of administering penicillin has been the most satisfactory. In some instances intermittent intramuscular administration may be equally satisfactory. However, if experience proves that larger doses are required for the intermittent intramuscular method than for the intravenous drip method, the former is not the one of choice at the present time. Penicillin should be reserved so far as possible for infections resistant to sulfonamide compounds. Penicillin therapy is no substitute for sound medical and surgical judgment in the treatment of bacterial infections.

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THE CLINICAL USE OF PENICILLIN

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In August 1943 penicillin supplied by the Office of Scientific Research and Development was made available, through the Committee on Chemotherapeutic and Other Agents [1] of the National Research Council, for clinical investigations at Stanford University Hospital. The ensuing report largely concerns our experiences with penicillin, with reference especially to continuous subcutaneous and intravenous infusions, since the subcutaneous and intravenous routes have not been extensively used by most investigators.

Penicillin has been furnished to us as the sodium salt. This is a brown or yellow powder, put up in sealed glass ampules, which is extremely soluble in water and in saline or dextrose solution; 10,000 units or more is readily taken up in 1 cc. of fluid. The material is unstable in the air and very hygroscopic; its potency is impaired by heat and in acid mediums.[2] Therefore the sealed ampules must be preserved in the refrigerator until used; however, a day's dose, made up in the proper solution, may safely be kept in the cold. Various lots of the sodium salt of penicillin have differed greatly in color when dissolved. The earlier batches especially yielded intensely yellow or even brownish solutions. The material more recently received has been almost colorless. It is our impression that these pale solutions contain less of certain impurities which may be associated with clinical reactions (see the following section).

The exact constitution of penicillin has not yet been worked out. Hence the material cannot be standardized by chemical means but is assayed by its biologic effect. The clumsy Florey (Oxford) unit—the amount of penicillin compared with an arbitrary standard which completely inhibits the growth of a test strain of Staphylococcus aureus—is still used and probably will hold its place until a chemically standardized product is available. In Florey's original material there were 40 to 50 units per milligram [3]; material which runs 700 to 1,000 units per milligram has now been prepared. Most of our material for which unitage was stated had a potency of about 300 units per milligram. A few other points should be kept in mind: first that penicillin, in large part at least, exercises a direct bactericidal action; second, that some preparations have immense potency and are effective in dilutions of over 1 to 100,000,000.

Those who have not actually worked with penicillin may have the idea that its use is a simple matter. This is not at all the case. We soon found that the

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Dr. Chester S. Keefer, chairman of the Committee on Therapeutic and Other Agents gave assistance and advice.

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1. Keefer, C. S., and others: Penicillin in the Treatment of Infections, J. A. M. A. **122**: 1217 (Aug. 28) 1943.
2. Abraham, E. P.; Chain. E., and Holiday, E. R.: Purification and Some Physical and Clinical Properties of Penicillin, Brit. J. Exper. Path. **23**: 103 (June) 1942.
3. Abraham, E. P., and others: Further Observations on Penicillin, Lancet **2**: 177 (Aug. 16) 1941.

patients should be housed in one physical unit and that a special "penicillin team" was necessary in order to carry out the treatments effectively. The duties of this team have been:

1. To answer numerous calls and to interview physicians desiring to send patients for penicillin therapy in regard to the suitability of these prospects.
2. To make preliminary examinations (physical and bacteriologic) in order to identify the infection and to establish proper records.
3. To plan the dosage and the route of penicillin therapy and to organize any ancillary treatment necessary in cooperation with surgeons, orthopedic physicians and other specialists.
4. To make up the total daily dose of penicillin for each patient in the desired amount and in the proper solvent. To keep records of the commercial lot used for each patient. To decide when treatment should be stopped.
5. To set up infusion sets and introduce needles for subcutaneous and for intravenous flow. To supervise the apparatus and see that it functions properly day and night.
6. To follow the clinical course and bacteriologic findings and plan therapy from day to day.
7. To measure blood levels of penicillin and the urinary excretion of the substance.
8. To keep and compile adequate records and to follow patients as long as necessary after treatment.

When 4 to 7 sick persons were under treatment at the same time the team found that they had their hands full. It is our feeling that at present best results will not be obtained by the occasional treatment of a single patient by a doctor not fully "at home" with the problems of penicillin therapy.

ROUTES AND TECHNIC OF ADMINISTRATION

Because of the rapid excretion of penicillin (see a later paragraph) frequent injections are necessary unless the material is given by continuous infusion. The standard procedure is to inject one eighth of the twenty-four hour dose deep into the gluteal (or other) muscle or into a vein every three hours day and night. Following an intravenous injection the blood level of penicillin promptly rises to a considerable height. According to the observations of Rammelkamp and Keefer [4] values of 1 or 2 Florey units per cubic centimeter of serum may be attained with a dose of 20,000 units, but there is a prompt drop so that within an hour or two barely measurable amounts remain. Following an intramuscular injection the blood level is lower but more sustained. At any rate it is to be noted that with intermittent injections one obtains peaks followed promptly by periods during which little if any penicillin remains in the blood stream. Whether such a state of affairs is less or more effective than a continuous, even if submaximal, blood level is not yet known. Both methods have produced satisfactory results, as will be pointed out.

One great disadvantage of injecting penicillin at three hour intervals is the inconvenience of this procedure. Either the doctor or a trained nurse must be available all night; if several patients are simultaneously under treatment it requires nearly the full time of some one to make the injections. Intramuscular injections are usually given with penicillin in high concentration—as much as 5,000 units per cubic centimeter of water or saline solution; they are not uncommonly followed by some local discomfort, and the patient also may be disturbed by the frequent needling. One man who was treated at various times by continuous subcutaneous and intravenous infusion and later by intermittent intramuscular injections objected to the latter procedure as the most annoying. Intermittent intravenous injections are usually arranged so that the dose (about 15,000 units) is given in 10 to 20 cc. of isotonic solution of sodium chloride.

Continuous Subcutaneous Infusion.—The subcutaneous administration of penicillin by the drip method has been extensively used in the Stanford clinic. The dose for a twenty-four hour period is prepared and given as follows:

Sterile 1,000 cc. bottles of isotonic solution of sodium chloride or 5 per cent dextrose are procured. We have used commercial products which are stated to be pyrogen free. If the dose for the day is 200,000 units or less, the total amount is dissolved in 1,000 cc. of fluid. We use saline solution unless there is a contraindication to the introduction of salt. The usual apparatus for subcutaneous clysis is set up with a dropper inserted so that the exact rate of flow of the solution can be checked. The system is filled with about 200 cc. of the penicillin solution, and the needle is introduced into the loose subcutaneous tissue of the thigh. The speed of flow is then so regulated that it will take twenty-four hours for the entire quantity of 1 or 2 liters to run in. If the total is 1,000 cc., the solution runs at approximately 10 drops per minute. Because of possible deterioration at room temperature, the bulk of the solution is kept in the refrigerator and from time to time amounts of 100 to 200 cc. are added to the solution in the infusion bottle. The attendants must watch the site of injection carefully to see that there is no large local collection of unabsorbed fluid; if collection occurs, the needle should be reinserted at another point. In our experience this rarely needs to be done oftener than every six to twelve or even twenty-four hours. A good deal of supervision of the whole procedure is necessary. The flow usually does not remain entirely constant over long periods; the number of drops per minute must be increased or decreased from time to time so as to consume as nearly as possible exactly twenty-four hours in introducing the entire dose. Before the subcutaneous drip is started we often give a single priming dose of 15,000 to 20,000 units into a vein to raise the blood level quickly.

Advantages and Objections to the Foregoing Method.—In some of the early cases especially the site of injection became extremely painful even when the flow was well regulated. As the solutions of penicillin are isotonic and neutral in reaction, the explanation was at first not clear. It is possible that some of the early lots of penicillin, which were highly colored (brownish yellow to yellow), contained irritating substances; there has been much less trouble with recent, more highly purified products which in the dilutions used have only a faint yellowish tinge. Small amounts of procaine hydrochloride added to the penicillin infusion also seem to have been effective in preventing local pain. In certain of the early cases there were sharp febrile reactions, the temperature rising to 39 to 40 C. (102.2 to 104.0 F.). Some of these reactions may have been due to pyrogenic saline solution or to stale infusion sets but more likely were caused also by impurities associated with the penicillin. Such reactions too are less frequent with recent lots.

The obvious advantages of continuous subcutaneous clysis are (1) the procedure once started is simple and can be watched by a nurse or other attendant, (2) it involves but little discomfort to the patient as frequent needling is avoided, and (3) the extremities do not have to be immobilized when the patient sleeps as they do with continuous intravenous drip. We have treated patients for several days to a week by the continuous subcutaneous drip without any technical difficulty.

The question of greatest importance is whether penicillin is as effective when given subcutaneously as

4. Rammelkamp, C. H., and Keefer, C. S.: The Absorption, Excretion and Distribution of Penicillin, J. Clin. Investigation **22**: 425 (May) 1943.

when introduced into the blood stream. Rammelkamp and Keefer [4] report the prompt recovery in the urine of about two thirds of intravenously injected penicillin. Observations in our clinic by Rantz and Kirby [5] indicate that under certain conditions the excretion of penicillin after intravenous injection approaches 100 per cent. It is possible that penicillin given subcutaneously may stay in the tissues longer and perhaps exercise some effect even though the blood levels are lower than after intravenous injections. This part of the subject is still under investigation, and much more work needs to be done. At any rate the values of penicillin per cubic centimeter of plasma [6] when 100,000 units is given in twenty-four hours are approximately 0.05 unit (subcutaneous clysis) and 0.10 unit (intravenous drip). It is our feeling at present that while the subcutaneous route is adequate in gonococcic and perhaps some other infections it should not be used in staphylococcic sepsis, in which relatively high blood levels are probably necessary in order to extirpate the infection. If the continuous intravenous drip cannot be given, intermittent intramuscular injections, perhaps combined with subcutaneous clysis, would be the best alternative.

Continuous Intravenous Injection.—The intravenous route for administering penicillin by the drip method seems to us the route of choice in severe septic infections. The preparation of the material and that of the apparatus are the same as for subcutaneous infusion except that an intravenous needle is used. With cooperative patients one can use the small veins of the hand or the foot; for the most part the only immobilization of the needle necessary is that obtained with a bit of adhesive tape and a light bandage; at night a splint is used. With restless, delirious or uncooperative subjects a partial cast is necessary.

Our earlier patients treated by intravenous drip often had violent febrile reactions. Bouts of this sort have been much less frequent with the recent lots of penicillin. In some of the early patients too thrombosis of veins occurred. This is now largely avoided by (1) availability of less irritating penicillin, (2) giving the material in no higher concentration than 100,000 units per liter and (3) not allowing the needle to stay more than twelve to twenty-four hours in the same vein. One patient became edematous after five days of intravenous therapy. It was calculated that he had received from 20 to 30 Gm. of sodium chloride daily; a change from saline to 5 per cent dextrose solution as a solvent for the sodium salt of penicillin was followed by disappearance of the swelling.

In 1 patient intrasternal drip was used. This method deserves further trial. We have employed a combination of methods in the same case, such as intravenous drip by day and subcutaneous infusion at night.

Penicillin is highly effective when injected into closed cavities in which the drug can be retained. In empyema, for example, the injection of 25,000 to 50,000 units may be followed by prompt sterilization, as in the following case:

CASE 1.—A 7 year old child had pneumococcic pneumonia about seven weeks before her entry into Stanford University Hospital. She had been treated with a sulfonamide compound without recovery. Empyema was diagnosed at that time but nothing further was done. On admission the child was prostrated, with typical signs of fluid in the left thoracic cavity, high irregular fever, serious anemia and leukocytosis. Fluid removed from the chest showed a pure growth of the type 1 pneumococcus. Thoracotomy was done and a tube inserted, but no improvement took place and the child seemed to be failing rapidly. On the sixth hospital day 30,000 units of penicillin in 50 cc. of saline solution was injected through the drainage tube, which was then closed with a clamp. Within twelve hours she was clinically well; her temperature was normal and remained so, and all fluids subsequently obtained from the chest were sterile. Several more doses of penicillin were injected through the tube, but they were probably unnecessary.

We have had no experience with injecting penicillin into infected joint cavities or intraspinally in meningitis. The treatment will doubtless be highly effective in certain cases. On the other hand, instillation of penicillin in chronic osteomyelitic sinuses has so far in our hands been useless, possibly because the organisms are not reached, possibly because the drug drains out before it acts in effective concentration. Tiny catheters inserted to the very depths of a sinus and flushed at frequent intervals with solutions of penicillin did not solve this problem.

DOSAGE

The dosage of penicillin has been largely arbitrary, and minimum effective amounts for various infections remain to be worked out. As long as the material is so difficult to prepare, economy is of the utmost importance. The penicillin commission at first advised that approximately 15,000 units be injected every three hours or roughly 100,000 units daily. We have used from 50,000 to 400,000 units daily in different situations largely on an empirical basis. Extensive studies by Rantz and Kirby [5] of blood levels following varying doses of penicillin show that even after continuous intravenous infusion at the rate of 20,000 units per hour plasma levels of only 0.4 to 0.5 Florey unit are obtained. With injection at the average rate of 100,000 units per day the level is only about 0.1 unit. As penicillin may be effective in the test tube in dilutions of over 1:100,000,000 it is impossible as yet to say definitely whether blood levels above some critical value increase therapeutic efficiency. However, Rammelkamp and Keefer [7] found that with staphylococcic infection a blood level of at least 0.15 unit per cubic centimeter is necessary to obtain maximum bactericidal effect. Our largest doses were given for serious staphylococcic infections, after previous experience had shown how difficult it is to extirpate the organisms, partly with the hope of quicker and more complete effect and partly with the idea that "drug fastness" of surviving germs would be less likely to occur. On the other hand, it seems clearly established that most patients with acute and subacute gonorrhea can be sterilized (of gonococci) and clinically cured in a period of one or two days by doses of from 50,000 to 200,000 units given by a number of routes.

In certain types of infections, as will be pointed out presently, it is extremely difficult to tell when the patient is cured. In staphylococcic sepsis, especially, bacteria may fail to grow in blood cultures, demonstrable lesions may heal, temperatures may decline or be normal and still within a few days after treatment is stopped blood cultures are again positive and lesions recur. This is especially true when bone is involved. In one case a particularly interesting phenomenon was

5. Rantz, L. A., and Kirby, W. M. M.: To be published.

6. The concentrations of penicillin in the blood and the urine were determined by a modification of the method of Rammelkamp (Proc. Soc. Exper. Biol. & Med. **51**: 95, 1942) and by a method devised by one of us (Kirby).

7. Rammelkamp, C. H., and Keefer, C. S.: Penicillin: Its Antibacterial Effect in Whole Blood and Serum for Hemolytic Streptococcus and Staphylococcus Aureus, J. Clin. Investigation **22**: 649 (Sept.) 1943.

observed. Blood cultures negative after treatment with penicillin was stopped became positive again after a few days even though the patient's temperature was practically normal. The staphylococci under these conditions grew out very slowly; the colonies were not visible until the seventh to tenth day, as if the organisms had been altered in some way, perhaps partially inhibited.

A final point in regard to dosage is whether it should vary with the age and the size of the patient. Here again there are no conclusive data but we are inclined to base the dosage mainly on the character and the severity of the infection.

TOXICITY

We have observed no toxic effects from penicillin. Thrombosis of veins and fever and local irritation caused by impurities, pyrogenic water or stale infusion sets have, as pointed out in an earlier paragraph, occurred at times but these do not seem to be essential effects of the drug. One is completely delivered from the sort of worry he has when using sulfonamide compounds or arsphenamines; there seems to be no injury of kidneys, liver, bone marrow or brain, and no cutaneous rashes have been seen in our cases with the exception of urticaria in 1 instance. Even such a large daily dose as 400,000 units is a minute fraction of the amount of penicillin which has been found to be toxic in animals.

RESULTS

Penicillin has been reported to be effective against infections with certain strains of the pneumococcus, the hemolytic streptococcus, the gonococcus, the meningococcus and the staphylococcus.[1] Some nonhemolytic streptococci seem to be little affected, and the result in Streptococcus viridans endocarditis has, like that with every other measure, been a failure. Unfortunately the colon-typhoid group seems definitely not affected. As to certain other organisms there have been conflicting reports; with regard to viruses and molds the full potentialities have not yet been explored. The material is said to be useless in malaria. In primary syphilis treponemes rapidly (in six to fifteen hours) disappear from surface lesions, which heal in ten days to two weeks; the ultimate results are of course not yet known.

Our experience has included infections with the gonococcus, the streptococcus, the pneumococcus, the staphylococcus and Treponema pallidum and can be best presented by illustrative case reports.

Gonococcic Infections.—It is now well established that penicillin is extremely effective in gonococcic infections.[8] It is especially useful in those in which the organisms have become resistant to the action of sulfonamide compounds. The following 2 cases show that even after infection has been present for months it can still be rapidly controlled:

CASE 2.—A 25 year old woman entered the hospital with a history of gonorrhea of two months' duration. For three weeks there had been excessive vaginal discharge, severe pain in the lower right quadrant of the abdomen and fever. Intensive treatment with sulfadiazine, hot douches and diathermy had failed to alleviate the condition. There was pronounced tenderness in the right lower quadrant and on pelvic examination there was tenderness in both adnexal regions. There was moderate leukocytosis, and many gonococci were grown in cultures of material from the cervix. The diagnosis was subacute gonococcic pelvic inflammatory disease, and 180,000 units of penicillin was given by subcutaneous infusion over a period of seventy-two hours. Within twenty-four hours after the start of treatment she felt well, the abdominal pain had practically disappeared, the temperature, which had been 100 F., fell to normal and cultures of material from the cervix were negative. On discharge from the hospital one week later she seemed entirely well.

The case illustrates very rapid cure in a woman of subacute, well intrenched gonococcic infection which had been resistant to all other modes of therapy. It is to be noted that the subcutaneous route was effective.

CASE 3.—A man aged 34 had been treated two months previously with full doses of sulfathiazole for acute anterior urethritis with an apparently good result. When seen by us there was only a trace of thin discharge with some tenderness of the epididymis. However, cultures of both urine and prostatic secretion yielded many colonies of gonococci. He was treated with 100,000 units of penicillin by continuous intravenous drip over a period of twenty-four hours, following which on two occasions cultures of urine and prostatic fluid yielded no gonococci. The clinical residue of symptoms promptly disappeared. There was decided improvement of his general well being.

A subacute gonococcic urethritis, prostatitis and epididymitis of two months' standing, resistant to treatment with sulfonamide compounds, was clinically and bacteriologically cured in twenty-four hours.

Another patient with fresh gonococcic urethritis and subacute arthritis of the wrist was promptly cured of his urethritis, but the arthritis persisted. The joint trouble had not been proved, however, to be gonococcic.

In summary, then, some of the most reliable and prompt results of penicillin therapy are obtained in patients with fresh or subacute gonococcic infection. In many patients, including those in whom the gonococci are resistant to treatment with sulfonamide compounds, a total quantity of 60,000 to 100,000 units given in divided doses intramuscularly or by continuous subcutaneous or intravenous drip is effective. Needless to say, a careful clinical and bacteriologic follow-up should be conducted on these patients preferably for several months.

Streptococcic Infections.—The wide field of streptococcic infections is only beginning to be explored. Hemolytic streptococci are perhaps less readily controlled than gonococci but are more easily controlled than staphylococci. This is a general statement subject to many exceptions depending on the type and the extent of the lesions. S. viridans, especially in subacute bacterial endocarditis, is little if at all affected. The following case shows, however, that penicillin may exert a favorable influence on a severe infection with nonhemolytic streptococci:

CASE 4.—A man 50 years old was hospitalized from June 14 to July 19, 1943 for treatment of a subphrenic abscess on the right side, which had probably developed on the basis of an undiagnosed rupture of the appendix. Following surgical drainage and administration of sulfadiazine he made what was believed to be an uneventful recovery. On August 20 he returned complaining that he had been ill with chills and fever for the three previous days. There were high "septic" fever and definite leukocytosis, but a blood culture was sterile. The abdomen was explored and at least three abscesses were found in the left lobe of the liver from which pus was recovered that yielded a pure growth of an anaerobic nonhemolytic streptococcus. The site of the old subdiaphragmatic abscess was explored and was found to contain a little pus. Both incisions were drained, and sulfadiazine was given, but the patient failed to improve. He was desperately ill, and since the organisms isolated from the hepatic abscesses were shown in vitro to be very sensitive to penicillin, administration of this material was

8. Mahoney, J. F.; Ferguson, C.; Buchholtz, M., and Van Slyke, C. J.: The Use of Penicillin Sodium in the Treatment of Sulfonamide Resistant Gonorrhea, Am. J. Syph., Gonor. & Ven. Dis. **27**: 525 (Sept.) 1943.

begun on the eighth hospital day. He received from 50,000 to 200,000 units daily, mostly by subcutaneous and intravenous routes, for seven days—a total of 600,000 units of penicillin being given. During treatment he seemed much improved generally but continued to have an irregular fever, the temperature rising to 102 to 104 F. daily. Soon after the penicillin therapy was discontinued, however, his temperature became lower; and since Escherichia coli was now demonstrated in the drainage from his incisions, sulfadiazine was again administered in the usual dosage. He improved steadily; his temperature became normal, and his incisions healed. He left the hospital on August 22, thirty-three days after the start of penicillin therapy. On October 15 he wrote enthusiastically that he was entirely well.

It is extremely difficult to evaluate the effect of penicillin in this case. It certainly did not produce an immediate cure, but it seemed to "turn the tide" in a patient who all observers felt was moribund.

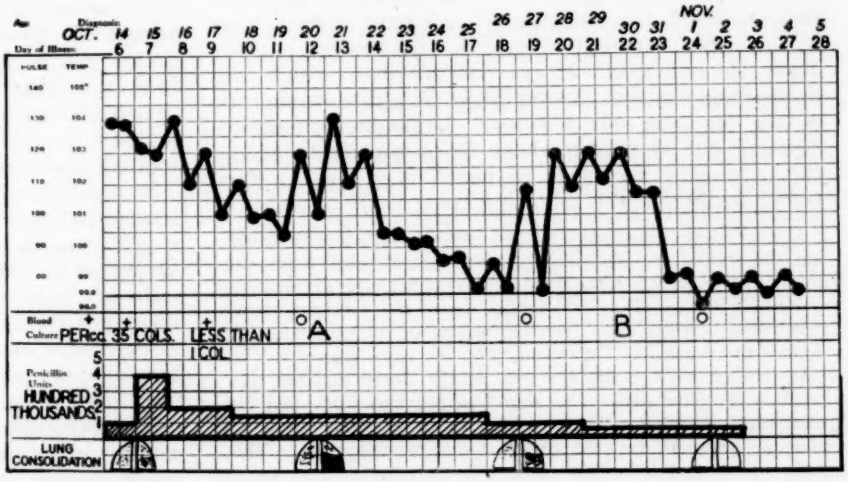
Staphylococcic Infections.—Staphylococcic infections, although undoubtedly responsive to penicillin, present an extremely difficult problem. In severe infections several weeks of intensive treatment may be necessary before a cure is achieved. Even then what appears to be a cure may be spurious, and organisms left dormant may revive and reinitiate active infection. The explanation of this peculiarity of staphylococci in relation to penicillin may be related to test tube experiments which have shown that even large doses of the drug fail to kill quite all the organisms if the inoculum is heavy. The theoretical aspects of this interesting fact have been discussed by Rammelkamp and Keefer [7] and others but cannot be gone into further here. It is also possible that surviving organisms may become penicillin resistant.

At any rate severe staphylococcic infections seem definitely to fall into two groups as regards response to penicillin. If the lesions are fresh and not walled off by heavy sinus tracts, or if they are accessible to thorough surgical evacuation, cures may be achieved even in desperately ill patients with multiple foci and bacteremia. If, on the other hand, chronic bone lesions, especially deep sinuses with thick walls and sluggish drainage, are present and cannot be surgically extirpated, it is much more difficult to accomplish anything.

Doses for staphylococcic infections must be considerably higher than those which are effective, for example, in gonorrhea. It is our feeling at present that for severe staphylococcic disease in an adult 300,000 to 400,000 units per day should be given until things are definitely on the mend and that a dosage of 150,000 to 200,000 units a day thereafter should be continued until the patient is well. Such doses are necessary to reach or surpass the blood level of 0.15 Florey unit per cubic centimeter of blood which Rammelkamp and Keefer [7] found to be necessary to achieve maximal killing of staphylococci in vitro. The intravenous rather than the subcutaneous route should be used for continuous infusion. If there is any contraindication to the introduction of large amounts of fluid, intramuscular injections of a concentrated solution of penicillin can be given. These principles are illustrated in the following cases.

CASE 5.—The patient was a 31 year old laborer who appeared moribund, and the history was obtained indirectly. Five days previously a carbuncle developed in the left scapular region. He rapidly became gravely ill with chills, fever, delirium and stupor. Two days later the carbuncle was incised, and he was given full doses of sulfathiazole. The blood culture was said to be positive. He did not respond and was sent into Stanford University Hospital. He was a red faced, sweating, dehydrated man, apparently dying. A huge fiery carbuncle with induration 20 cm. in diameter had been incised, and there was drainage of thin pus from which Staph. aureus was grown. There were scars of small furuncles on the right hand and arm. The respirations varied from 50 to 80 per minute, and there was dulness at the base of the right lung with many rales, and scattered patches of rales were heard through both lungs. The leukocyte count was 18,000, and the blood on culture yielded 35 colonies of Staph. aureus (coagulose positive) per cubic centimeter. The diagnosis was staphylococcic sepsis with bacteremia, carbuncle and extensive staphylococcic pneumonia (metastatic).

Penicillin was given by intravenous drip at the rate of 400,000 units for the first day, later decreasing (see chart) to 150,000 units and finally to 50,000 to 60,000 units daily. A total of 2,560,000 units was given over a period of twenty days. For the first nine days there was no notable improvement although



Course in case 5.

the patient seemed a little less toxic. The carbuncle resolved steadily, but pneumonia continued and there were frank signs of solidification of the lower lobe of the right lung. On the ninth day there was amazing improvement; the temperature fell rapidly, the patient became bright and said he felt well, and the signs of disease in the lungs began to resolve. By the twelfth day the temperature was normal. From the fifteenth to the seventeenth day elevations up to 39.5 C. (103.1 F.) recurred, but the temperature dropped immediately when a fresh infusion set was used. By the twentieth day he seemed cured; the lungs were almost clear, the carbuncle was healed and the temperature was normal. The accompanying chart shows his course graphically.

This is the sort of staphylococcic infection, sulfathiazole resistant and almost invariably fatal, which may respond brilliantly to penicillin. Note that there were no old walled off lesions. Two other points are important: In spite of large doses of penicillin there was not much change for over a week; this is the rule in staphylococcic sepsis of this type, contrasting with the "overnight" cure of gonorrhea. Infusion sets should be changed frequently, as molds and other organisms may grow in penicillin and produce pyrogenic material.

CASE 6.—A 15 year old boy entered the hospital for penicillin therapy because of chronic osteomyelitis. Lesions had been recurring for twenty-six months, involving the left ankle, knee and groin, the right ankle and thigh and the back. On entry

there were three sinuses draining greenish pus from which Staph. aureus (coagulase positive) was grown. One sinus ran deep into the spine. All were associated with chronic destructive lesions in bone, as definitely shown in roentgenograms. There had been numerous surgical operations in the past. He was a chubby boy, slightly pale. Physical examination showed nothing remarkable except the scars and sinuses. There were slight elevations of temperature and slight anemia (hemoglobin content 72 per cent, Sahli). Between September 21 and November 1 he received 2,225,000 units of penicillin mostly by intravenous drip but at times by subcutaneous clysis. The daily dose varied from 60,000 to 200,000 units. Between October 8 and 18 about 40,000 units in a solution of 100 units per cubic centimeter of saline solution was injected deep into the anterior sinus (5 cc. every three hours).

The results of all this treatment were disappointing. Drainage was not lessened, sinuses did not close, and cultures remained positive.

In this case low grade staphylococcic sepsis and multiple osteomyelitic sinuses with thick walls failed to respond to penicillin therapy. It is possible that larger doses over a longer period would accomplish more, and further intensive therapy is planned in connection with an operation for removal of a sequestrum. At best, however, the problem is much more difficult than in the type presented in case 5. In another case an acute staphylococcic abscess of an arm, which was opened and drained, cleared up, while a chronic sinusitis of the leg was not affected. Undoubtedly surgical cleaning out of necrotic bone helps greatly to render the organisms accessible to penicillin. This is illustrated further in the following case:

CASE 7.—A woman aged 32 had had chronic sinusitis involving the frontal and maxillary sinuses for at least four years. Four weeks before entry the right antrum was drained, and one week later swelling and tenderness of the overlying tissues developed. Seven days' administration of sulfonamide compounds did not help. On examination the right side of the face was swollen so that the eye was nearly closed and the nasolabial fold obliterated. The skin was red and shiny and very tender on pressure. There was a draining sinus above the alveolar process over the canine tooth on the right. Thick yellow pus came from this area. The alveolar process seemed to be loose. The diagnosis was osteomyelitis of the right maxilla. Culture showed a variety of bacteria including a heavy growth of Staph. aureus (coagulase positive). There were swings of the temperature up to 39.5 C. (103.1 F.).

Otolaryngologists as consultants pointed out that in their experience bone infections of this sort always progress to a fatal issue. Between September 25 and October 31 the patient received 2,690,000 units of penicillin by intravenous and subcutaneous drip in doses of 45,000 to 200,000 units daily. Two operations were performed for the removal of necrotic pieces of bone. Her disease ran a stormy course with several exacerbations, but by November 1 the temperature was normal. It has now remained normal for twelve days, she feels well, all drains are removed and the sinuses are closing.

The importance of a combination of surgical drainage and removal of dead bone with the continuous injection of penicillin is to be emphasized. In spite of the treatment with penicillin this patient continued to have exacerbations until such surgical measures had been instituted. On the other hand, it is said that surgical treatment alone never arrests the relentless progress of osteomyelitis in patients with involvement of bones of the face of this type.

SYPHILIS

The rapid disappearance of Treponema pallidum from surface lesions and the resolution of early lesions under penicillin therapy have recently been reported.[9] These observations we have confirmed without exception in a series of 7 cases of early (seronegative and seropositive) syphilis. A typical example is as follows:

CASE 8.—A young Negro noticed a penile lesion fourteen days and swollen glands in the groins two days before entering the hospital. He had a typical chancre, 1.2 cm. in diameter, and large inguinal lymph nodes. The Wassermann reaction was negative, but huge numbers of typical, actively motile treponemes were seen in dark field preparations from the primary lesion. He received 200,000 units of penicillin by intravenous drip daily for five days—a total of 1,000,000 units. Twelve hours after the start of treatment only a rare treponeme was seen; two hours later none were found. There was rapid involution of the chancre and nodes over a period of ten days.

In other cases condylomas have become free of treponemes in approximately twelve to twenty hours. In 1 patient with an extensive but pale roseola there was a violent flare-up of all the lesions within a few hours after the infusion of penicillin was started, a phenomenon probably analogous to the Herxheimer reaction. The lesions became bright red and palpable. This was followed by rapid clearing.

It seems clear then that immediate results comparable to those obtained with full doses of arsphenamine can be achieved. However, this by no means indicates that treponemes have been completely destroyed throughout the body and that recurrences, perhaps resembling those seen in patients inadequately treated with arsphenamine, will not take place later. The most careful observation and control of penicillin treated patients are necessary for a long period before any conclusion can be drawn as to the ultimate effect. Quantitative serologic tests at frequent intervals, thorough physical examination and later examination of the spinal fluid must all be done over a period of years to determine the final results. Dosage also has so far been purely tentative. It is clear, then, promising as these immediate results in syphilis seem to be, that the use of penicillin should still be restricted to the most careful experimental study of selected cases. The whole matter of penicillin treatment for syphilis is now being supervised by committees of the National Research Council and by the Committee on Medical Research of the Office of Scientific Research and Development.

COMMENT AND SUMMARY

These experiences with penicillin therapy serve largely to emphasize the unsolved problems. The best route of administration and the optimum dosage of penicillin for various infections are as yet unsettled. Formulation of a sort is however possible. It is established that gonococcic infections can usually be cured in a day or so by a total dose of 60,000 to 100,000 units given by intravenous drip, by subcutaneous clysis or by divided intramuscular injection. Staphylococcic infections, on the other hand, are much more stubborn and even in favorable cases days or weeks elapse before cure is effected. It is our impression that a much higher dose of penicillin (200,000 to 400,000 units per day) should be given in the early stages of severe staphylococcic infection and that the dose should never be under 120,000 units for an adult of average size. Continuous intravenous drip has been successful in our hands in staphylococcic infections whereas subcutaneous clysis is likely to be ineffective because of the lower blood levels obtained by this method, although the last word on the subject is not yet said. Intermittent intramuscular injections seem to us a less satisfactory method of treating severe staphylococcic sepsis.

9. Mahoney, J. F.: Paper read before the American Public Health Association.

but our experience is mainly with intravenous administration. In any event, in every case the dose of penicillin and the route of administration should be carefully planned each day. One is guided by the clinical situation, the bacteriologic findings and the measurements of the blood level of penicillin. These principles apply to any infection for which penicillin is used.

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ANTIMICROBIAL AGENTS OF BIOLOGIC ORIGIN

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From the point of view of chemotherapy knowledge of the origin of an antimicrobial agent is less important than an understanding of its nature and of its chemical and biologic properties. Quinine and penicillin are obtained today from biologic sources; tomorrow they may be synthesized in the chemical laboratory; but whatever their mode of production, the student of infectious diseases will remain primarily concerned with their specificity for certain strains and stages of parasites, the mechanism of their action on the susceptible cells and their physiologic and pathologic effects on the host.

During the past few years great and perhaps excessive emphasis has been placed on micro-organisms as sources of antimicrobial agents. It must be kept in mind, however, that the production of these agents is not an exclusive attribute of micro-organisms but is widely distributed in the plant and animal kingdom.[1] Suffice it to mention that among plant products quinine, emetine, chaulmoogra oil and many other substances were used in therapy long before the bacteriologic era and have, in fact, remained the best chemotherapeutic agents available for certain specific purposes. From animal tissues and body fluids there have been separated a great variety of products which possess interesting antibacterial properties. One of these, lactenin, has been obtained from milk in the albumin fraction; it appears to be a protein and exhibits great activity against streptococci;[2] another substance, lysozyme, which will be mentioned again later in this report, causes the lysis of several bacterial species;[3] histones and protamines have also been recently shown to possess antibacterial properties.[4] Lactenin and lysozyme have not yet found application in the treatment of infectious diseases but they may be of significance in preventing certain types of infections, as will be pointed out later.

The number and the variety of antimicrobial agents produced by unrelated strains of micro-organisms are illustrated by a recent review which lists 373 references dealing with this subject.[5] These microbial products include simple organic molecules like hydrogen peroxide, pigments like pyocyanine (*a*-oxyphenazine), many phenols and quinones, complex organic substances like penicillin, polypeptides like gramicidin and tyrocidine, and protein enzymes like penatin.

Although many of these substances of biologic origin exhibit great antiseptic activity in vitro, only a few retain this property in the presence of animal tissues; in this respect antiseptics of biologic origin present the same problem as chemical antiseptics. Of the countless antimicrobial substances produced by chemical methods (heavy metals, halogen derivatives and other oxidizing agents, phenolic substances, dyes, aromatic oils, soaps and detergents, and others) only a limited number, such as some arsenicals and the sulfonamides, can be classified as chemotherapeutic agents. It would be of the greatest theoretical and practical interest, therefore, to understand the nature of that property or combination of properties which permits an antimicrobial agent—be it of chemical or of biologic origin—to retain its activity in vivo. Leaving out of consideration most of the factors which involve the host, one may attempt to recognize some of the properties which differentiate the ordinary antiseptics from the few substances which can be used in the therapy of infectious diseases. It may be useful, however, to begin by defining more accurately some of the phenomena by which one recognizes the antiseptic effect of a certain substance on a given microbial species.

BACTERIOSTATIC VS. BACTERICIDAL EFFECT

Antimicrobial agents are usually described as possessing a bacteriostatic or a bactericidal effect. The sulfonamides and penicillin offer perfect examples of the former type of action; even when used in concentrations greatly in excess of those sufficient to cause complete inhibition of growth they fail to cause rapid death of even the most susceptible species. Moreover, when the susceptible organisms which have been exposed to the drug are transferred to a new medium free from it, they grow as readily as untreated cells. On the other hand, phenols and actinomycin B,[6] for instance, are typical representatives of the bactericidal group; in adequate concentrations they cause within a few minutes the death of cells exposed to their solutions. In the typical cases one can therefore differentiate without any difficulty bacteriostatic and bactericidal effects. There are many situations, however, where the differentiation is less clear. One may consider, for example, the case of a suspension of staphylococci or of anthrax spores treated with mercury bichloride; after being exposed for a few hours to the antiseptic these cells fail to grow when transferred to a new medium. If, however, the poisoned culture is treated with hydrogen sulfide, the cells recover their viability even though they have been exposed for seventy-two hours to 1 per cent mercury bichloride.[7] A similar phenomenon is observed with a certain basic protein extracted from wheat germ which acts as a powerful antiseptic for yeast and for Lactobacillus casei. If after twenty-four hours' exposure of these organisms to the toxic protein one adds to the system an adequate amount of a phosphatide, the cells recover their viability and grow; it appears that in this case the wheat protein forms a lipoprotein complex with the phospholipid and is thus dissociated from the inhibited microbial cell.[8] As a final example of reversible inhibition, one may consider the case of a gram positive organism which after treatment with gentian

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violet appears to have lost its ability to grow; in this case again it is sufficient to add to the system the proper amount of acid—large enough to permit dissociation of the dye-bacteria complex but not too great to interfere with bacterial growth—to observe that the effect was only bacteriostatic.[9]

A statement of the problem of bacteriostatic versus bactericidal effect can be presented in the following general terms. A reversible combination takes place between some cellular constituent of the bacterial cell and the antiseptic.

$$\text{Bacteria} + \text{Antiseptic} \rightleftarrows \text{Bacteria} - \text{Antiseptic Complex}$$

The equilibrium of this reaction is conditioned not only by the nature of the microbial species and of the antiseptic involved but also by the environmental conditions under which the reaction takes place. Thus, if bacteria and antiseptic combine through their basic and acidic groups, the p_H of the medium is of the greatest importance, and in fact it is known that cationic antimicrobial agents in general, and basic dyes in particular, are most active at slightly alkaline reactions, whereas the antiseptic effect of anionic detergents and dyes is enhanced in acid mediums.[10] One may, on the other hand, affect the equilibrium by adding to the system a substance which possesses great affinity for the antimicrobial agent (e. g. SH-compounds for arsenicals and mercurials, phospholipids for the wheat protein) and thus help in dissociating the antiseptic-bacteria complex.

According to these views it may not be appropriate to speak of a substance as bactericidal or bacteriostatic in nature, since the outcome—bactericidal or bacteriostatic—of the reaction caused by any given agent is conditioned not only by the chemical nature of the latter but also by the nature of the micro-organism under consideration and by the environmental factors. It is obvious, however, that there are some characteristics of the antimicrobial agent which are of paramount importance in deciding its action; thus substances endowed with surface activity are likely to form with the microbial cell fairly stable complexes and therefore to behave as bactericidal agents. Moreover, the property of surface activity probably results in disruption of cell membranes and denaturation of protein enzymes, thus causing irreversible damage and death.[11] It is perhaps to their ability to lower surface tension that substances like the phenols, the anionic and cationic detergents, and tyrocidine owe their great bactericidal activity.[11a]

INHIBITORS OF ANTIMICROBIAL AGENTS

It is hardly necessary to mention that the same factors which are capable of reversing the reaction between cell and antiseptic and of restoring, therefore, viability to an inhibited cell are also capable of inhibiting entirely the antiseptic effect of a given substance if added to the microbial suspension prior to the antiseptic. It is common knowledge that paraaminobenzoic acid inhibits the antibacterial effect of sulfonamides, probably by competing with the drug for some specific cellular substrate; other similar examples of competitive inhibition have been described and need not be referred to further here.[11b] There is, however, a type of inhibition of antimicrobial agents which is still poorly understood and deserves some mention at the present time. It has been observed that several types of phospholipids and a few other surface active substances when added to a suspension of living cells are capable of protecting them against the lethal effect of the subsequent addition of many toxic agents; it has already been seen that phospholipids can form inert complexes with certain toxic agents (wheat protein). It is likely that they can also exert a protective action by becoming adsorbed on the cell surface, perhaps at the very sites at which the toxic agents would otherwise become adsorbed;[12] this fact is of great practical importance since phospholipids are so commonly present in biologic materials. It has been found, for instance, that the presence of very small amounts of a cephalin such as phosphatidyl serine is sufficient to protect susceptible bacterial species against the action of gramicidin not only in vitro but also in vivo; in this respect it is worth pointing out that gram negative bacilli release into the mediums in which they grow certain complexes rich in phospholipids which behave as extremely active inhibitors of gramicidin; this observation probably explains the fact that in mixed cultures or mixed infections the gram negative bacilli appear to protect the otherwise susceptible gram positive organisms against the effect of gramicidin.[13] Although penicillin is readily inactivated by chemical procedures and by certain microbial enzymes, there is as yet no record of any other biologic material capable of inhibiting its action, a fact which certainly contributes to the remarkable effectiveness of the drug in vivo.[14]

THE SELECTIVITY OF CHEMOTHERAPEUTIC AGENTS

The ideal chemotherapeutic agent is, of course, one which exhibits great affinity for the parasites but is completely inactive against the constituents of the tissues of the host. On the other hand, it is well known that most antimicrobial agents, whether of synthetic or of biologic origin, affect all kinds of living cells, reacting with morphologic structures or with metabolic systems common to all living matter and behaving, in other words, as general protoplasmic poisons. It is of special interest, therefore, that several of the few agents which have proved to retain their activity in vivo usually exhibit definite selectivity in their action. Thus penicillin, which is so immensely active against certain types of organisms (gram positive cocci, bacilli, gonococci, spirochetes) is only little active or inactive even in vitro against many gram negative and acid fast bacilli;[15] little has been published so far as to its effect on the cells of animal tissues, but isolated reports indicate that it does not affect their growth or metabolism, a fact reflected in the remarkable lack of toxicity of penicillin. Gramicidin also exhibits great selectivity as to microbial species that it affects and in general is most active against gram positive species (gonococci and meningococci being also somewhat susceptible); gramicidin is also extremely toxic for erythrocytes and for spermatozoa but is apparently inactive against the other types of animal cells so far tested;[16]

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its hemolytic property is sufficient to rule out its use in the treatment of systemic infections but its lack of toxicity for other cells, especially those involved in tissue repair, may render it useful in the treatment of certain localized infections; this is illustrated by the many reports of its successful utilization in the treatment of bovine mastitis caused by streptococci [17] and of infected ulcers. Even the sulfonamides are not equally active against all types of cells, and it is perhaps of some interest that among the gram negative bacilli those of the dysentery group are the ones which have proved most susceptible; interestingly enough the dysentery bacilli have been classified by some authors as "gram variable" and are in fact, by some of their properties, closer to the gram positive group than are the organisms of the colon-typhoid group.

It is obvious that many factors influence the selectivity of an antimicrobial agent: the acidic and basic properties of the cell under consideration, the nature and property of its membrane, its permeability, the relative importance for metabolism and viability of the specific biochemical systems affected by the antiseptic, the activity of the autolytic enzymes, and so on, are all attributes which bear a definite relation to susceptibility. Moreover, each one of these properties may undergo variation either independently or simultaneously and thus give rise to mutant forms of modified susceptibility. It is because so many and unrelated factors affect the outcome of the antiseptic and chemotherapeutic reaction that the receptor concept of Paul Ehrlich, although correct in its general principle, has been relatively ineffective for the analysis of the problem. Among the few generalizations which appear justified at the present time, it may be appropriate to mention that certain gram negative bacilli in their behavior toward many types of antiseptics behave much more like animal tissue cells than do other microorganisms. If confirmed, this view would provide an explanation for the fact that attempts to discover chemotherapeutic agents effective against Salmonella have so far presented such great difficulties.

THE EFFECT OF ANTISEPTICS AND CHEMOTHERAPEUTIC AGENTS ON CELLULAR METABOLISM

It is known that most antiseptics interrupt immediately and irreversibly the metabolism of living cells, whether it is measured in terms of oxygen consumption, production of carbon dioxide, production of acid, luminescence or some other manifestation; in fact, measurement of the inhibition of these metabolic events has often been suggested as a quantitative method of determining antiseptic action. One may consider on the other hand what little is known of the effect on metabolism of some of the few agents which have been found to retain their activity in vivo. There is still much argument concerning the intimate mechanism of the action of sulfonamides; it is certain, however, that these drugs do not completely or even noticeably interrupt cellular metabolism; bacterial cells inhibited in their growth continue to metabolize even in the presence of an excess of sulfanilamide.[18] Although no quantitative data have yet been published concerning the effect of penicillin on the metabolism of susceptible cells, it has been clearly stated that the drug does not affect the respiration of staphylococci. The comparative effect of gramicidin and tyrocidine is illuminating with reference to this problem. Both these substances are produced in cultures of Bacillus brevis, both are polypeptides in nature, both exhibit antibacterial activity. Tyrocidine is toxic not only for bacteria but also for all types of living cells so far tested and is therefore entirely ineffective in vitro; gramicidin, on the contrary, although toxic for spermatozoa and erythrocytes, is inactive against many other types of tissue cells and, among bacteria, affects chiefly the gram positive species. Interestingly enough tyrocidine, like other common antiseptics, completely and irreversibly inhibits cellular metabolism, whereas gramicidin permits maintenance—even though in a modified form—of oxygen consumption, of carbon dioxide and acid production and of several other metabolic functions of the most susceptible cells.[19]

It appears, therefore, that the typical antiseptic behaves as a gross protoplasmic poison, destroying the general metabolic—and especially the catabolic—cellular mechanisms. On the contrary, most chemotherapeutic agents have a very selective effect on some specific metabolic steps. The nature of the specific steps inhibited will undoubtedly vary from one chemotherapeutic agent to another. There are, for instance, observations which suggest that the primary effect of the sulfonamides is on some synthetic anabolic process.[20] In the case of penicillin it is reported that the drug does not in reality interrupt growth of the inhibited cell but prevents cellular division, with the frequent production of giant forms.[21] In this case, therefore, the inhibition may affect some step of cellular division and not a catabolic process measured by respiration.

The analysis of the differential effect of common antiseptics and chemotherapeutic agents on cellular metabolism is a problem not only of theoretical interest but also of immediate practical importance. Because of the cost and the labor involved in animal experimentation, many workers have attempted to develop short cut "screening" methods for the rapid detection in vitro of antimicrobial agents in natural sources. All of these methods make use of inhibition of metabolism as measured by the uptake of the oxygen, production of carbon dioxide or of acid, luminescence and other manifestations. It is important to realize that, although these technics would have been successful in detecting the gross protoplasmic poisons they would probably have failed in recognizing many substances of chemotherapeutic activity; penicillin would have been neglected in favor of the countless other phenolic compounds and quinones produced by molds, actinomycetes and bacteria; tyrocidine would have been selected in preference to gramicidin; the sulfonamides would have been discarded as agents of little metabolic activity.[21a] The need for in vitro screening methods in the search for new chemotherapeutic agents is evident; it is clear, however, that none of the methods available at the present time are satisfactory and that the development of new and adequate technics may have to await increased knowledge of the reactions concerned in anabolic metabolism and in the processes of growth and cellular division.

17. Little, R. B., in Sixteenth Annual Report of the New York State Association of Milk Sanitarians, 1942, p. 107.
18. Dubos.[1] Van Niel.[20]
19. Hotchkiss, R. D.: Recent Advances in Enzymology, to be published. Hotchkiss, R. D.; Dubos, R. J., and Coburn, A. F.: J. Biol. Chem. **146**: 421, 1942. Dubos and Hotchkiss.[16]
20. Van Niel, C. B., in Luck, J. M.: Annual Review of Biochemistry, Stanford University, Calif., Annual Reviews, Inc., 1943, vol. 12, p. 551.
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21a. Rake, G.; McKee, C. M., and Jones, H.: Proc. Soc. Exper. Biol. & Med. **51**: 273, 1942.

EFFECT OF ENZYMES ON CERTAIN CELLULAR CONSTITUENTS AND PRODUCTS

So far I have limited discussion to those substances which directly or indirectly affect the catabolic and anabolic activities of micro-organisms. It is among these substances that the most effective agents for the treatment of infectious diseases have been found. It may be worth while, however, were it only as a bid to the future, to mention at this time that there is another group of agents of biologic origin—namely enzymes—which are capable of destroying certain structural components or certain products of living infectious organisms and thereby modifying their pathogenicity.

Lysozyme, for instance, is an enzyme present in a great variety of animal tissues (and perhaps in plant tissues as well); it causes lysis of the cells of many bacterial species by hydrolyzing some mucopolysaccharide which is an essential structural constituent of the susceptible cells.[22] It is true that lysozyme is most active against nonpathogenic species and is therefore not used in therapy. One may wonder, however, whether certain strains of bacteria which are potentially pathogenic are not prevented from establishing an infection precisely because they are susceptible to lysozyme, a normal constituent of many tissues; in other words, lysozyme may function as one of the many mechanisms which protect the animal body against microbial invasion. The fact that an enzyme like lysozyme can act on the living cells of certain microbial species also suggests the possibility of finding enzymes active against the structural components of pathogenic species. That such enzymes exist somewhere in the living world can be taken for granted, and search for their discovery would be an interesting venture, perhaps rewarding in practical results.

Lysozyme attacks a chemical component so essential to the integrity of cellular structure that it causes lysis and death of the susceptible cells. To affect the pathogenic career of an infectious micro-organism, however, it may be sufficient to attack a product of the micro-organism not essential to its vital activities but of critical importance for its pathogenicity. Thus there have been obtained from saprophytic micro-organisms, also from leech extract, enzymes capable of hydrolyzing the capsular polysaccharides of pneumococci and streptococci. Destruction of these capsular materials by the enzymes does not affect the viability, the metabolism or the growth in vitro of the pneumococci or the streptococci concerned. It results, however, in the removal from the periphery of the bacterial cell of a substance—the capsular polysaccharide—which protects the cell against phagocytosis. In fact, when experimental animals are infected with virulent pneumococci and then treated with the proper polysaccharidase, the infective bacteria present in the body fluids rapidly lose their capsules and undergo phagocytosis, a cycle of events which culminates in recovery from the infection.[23] Whether the principle which has thus been established is applicable to other types of infection is, of course, a moot question. These facts, however, establish clearly that to interfere with the pathogenic career of a parasite it is not indispensable to exert on it an injury affecting its viability; it is sufficient to attack some component or product of the cell which conditions pathogenicity.

22. Meyer, K.; Thompson, R.; Palmer, J. W., and Khorazo, D.: J. Biol. Chem. **113**:303, 1936. Fleming.[3]
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CONCLUSIONS

Present knowledge of the factors—both qualitative and quantitative—which differentiate the common antiseptics from the few substances which behave as chemotherapeutic agents is far too meager to permit a general statement of the problem. In a general way, however, it may be justified to state that, in contrast with general protoplasmic poisons, chemotherapeutic agents exhibit selectivity not only with reference to the type of cells which they affect but also with reference to the metabolic systems or structural constituents with which they react.

Antimicrobial agents obtained from natural sources—from animals, plants or micro-organisms—have revealed certain types of organic structures of unsuspected biologic activities; they will certainly give to the chemist and the biologist important clues for the preparation and the study of new biologically active agents. It must be kept in mind, however, that the origin of a substance is relatively unimportant in determining its properties; indeed, it will be noticed that in the foregoing pages the different problems of antisepsis and chemotherapy could be illustrated equally well by selecting examples from the field of chemical substances or from that of agents derived from biologic sources. Most antiseptics of biologic origin, like those prepared by chemical methods, are protoplasmic poisons and of little interest for chemotherapy; as already stated, the most urgent problem is not the discovery of more and more antiseptics but the definition of that property or more likely combination of properties which determine whether a certain agent will retain its antimicrobial activity in the presence of animal tissues without injury to the latter. It is certain that a more complete understanding of this problem will help not only in the search for new chemotherapeutic substances but also in the rational utilization of those already available.

ABSTRACT OF DISCUSSION

ON PAPERS OF DRS. DAWSON AND HOBBY, DR. HERRELL, DRS. BLOOMFIELD, RANTZ, AND KIRBY AND DR. DUBOS

DR. CHESTER S. KEEFER, Boston: This symposium focuses attention on a group of antimicrobial agents of biologic origin, with special emphasis on penicillin. Dr. Dubos states the problem directly when he says that the most urgent problem is not the discovery of more and more antiseptics but the definition of the combination of properties which determine whether a certain agent will retain its antimicrobial activity in the presence of animal tissues without injury. The discussion of the clinical use of penicillin by Dawson and Hobby, Bloomfield, Kirby and Rantz, and Herrell summarizes the experience of three groups of highly qualified investigators. There is general agreement concerning the diseases in which penicillin is an effective agent. Penicillin causes few, if any, toxic or undesirable reactions, but, as Bloomfield and his associates point out, there are many unsolved problems. The points about which there is no universal agreement are the questions of dosage, the best method of administration and the duration of the treatment. The final answer will resolve itself with the study of more cases. From the analysis of 1,500 cases which have been reported to the Committee on Chemotherapeutic and Other Agents of the National Research Council, it is clear that the dosage recom-

mended by Dr. Herrell will be adequate in some cases but totally inadequate in many others. While Dr. Dawson recommends somewhat larger doses than Herrell, he has recommended somewhat smaller doses than those recommended by Bloomfield and his associates and by the Committee on Chemotherapeutic and Other Agents of the National Research Council. With regard to subacute bacterial endocarditis, the picture is confused. Of the 55 cases of bacterial endocarditis reported to our committee, only 3 patients are alive after one year of study. Patient 10 of Dr. Dawson received the largest amount of penicillin, and while the immediate cause of death was a cerebral embolus the blood cultures were still positive at the time of death. I am familiar with other cases in which the total amount of penicillin used has been over 20 million units and the patients are still ill or have died after a period of months. A recent report by Loewe and his associates records temporary improvement in 7 cases; in the 8th case, not included in the report, more than 8 million units of penicillin was administered over a period of two months without improvement. There may be a temporary sterilization of the blood stream and a decrease in the fever following the use of penicillin in some cases of bacterial endocarditis. It is possible that in a few the improvement may be permanent. At the present time it is not known how often this may occur. With the introduction of penicillin a new antibacterial agent of great potency has been added to our list of effective therapeutic agents, and it will save many lives and shorten the course of many infections.

DR. WALTER S. PRIEST, Chicago: This timely symposium should clarify professional thinking regarding penicillin. The public and the lay press are not alone in regarding the drug as a cureall, a tendency which leads to unfortunate situations. In these reports and the report of Dr. Keefer (THE JOURNAL, Aug. 28, 1943, p. 1217) are included all the infections in which penicillin is known to be of definite value so far. Encouraging results have been obtained in early syphilis and gas gangrene, but more information is necessary. The adequacy of dosage in previously reported failures in subacute bacterial endocarditis was open to question. Dawson's experience (table 5), Loewe's report (THE JOURNAL, Jan. 15, 1944, p. 144) and my own experience suggest that something may be accomplished by doses of 150,000 to 200,000 units a day over two or more weeks. Restudy of this problem is at present under way. Results so far, while encouraging, do not justify the dogmatic and glowing statements appearing in some newspapers. With the exception of gonorrhea, complete agreement as to dosage is lacking. Success with 20,000 to 40,000 units a day against a given organism is obtained by one observer, while another found up to 400,000 units necessary. Some of the failures may have been due to inadequate blood levels. General agreement as to method of administration likewise has not been reached. Because of the few injections required in treating gonorrhea, intramuscular injection is the method of choice. In other infections we prefer the continuous intravenous drip method when the patient's psychic reaction and availability of superficial veins permit. The needle has been left in situ for days without ill effect, using distilled water with or without 5 per cent dextrose. Concentrations of 200,000 to 400,000 units per liter have been used. Unless it can be shown that higher blood levels can be continuously maintained with less penicillin by continuous subcutaneous infusion, there would seem to be little advantage in this method. I have assayed solutions used in continuous twenty-four hour drip and have found no decrease in potency at the end of the period. The recent experiences with larger doses confirm the earlier impression of the nontoxicity of penicillin. I have given 500,000 units in 100 cc. of water intravenously over thirty minutes and 40,000 units in 5 cc. of saline solution intrathecally without significant reaction. No toxic reaction followed administration of 1,000,000 units of the calcium salt intravenously over seven days. Some observations indicate a bactericidal effect of penicillin, but these are too limited to permit of definite conclusions. Drs. Dawson and Bloomfield refer to it as a bactericidal agent, while Dr. Dubos considers its action primarily bacteriostatic.

RELAPSES IN PERNICIOUS ANEMIA

STEVEN O. SCHWARTZ, M.D.
AND
HELEN LEGERE
CHICAGO

Before the introduction of liver therapy pernicious anemia was known as "a chronic malady with remarkable remissions."[1] The literature is studded with reports of unusually long remissions. Of Cabot's[2] 1,200 patients, 10 lived seven years or more between relapses, while 6 were considered as having recovered.[3] Ten well authenticated cases have been reported with spontaneous remissions lasting ten years or more (table 1). Multiple relapses were not uncommon either, though few patients survived their third. According to Cabot, about 56 per cent had one spontaneous remission, 23 per cent had two, 12 per cent had three, 4 per cent had four and 4 per cent had five, each one lasting from three months to four years.

This report is based on the observation of 54 patients with 88 individual self-induced relapses brought about by discontinuance of therapy, either immediately after release from the hospital or months or even years after satisfactory maintenance had been established (table 2).

TABLE 1.—*Authenticated Cases of Pernicious Anemia Lasting Ten Years or More* *

Author	Year of Report	Duration of Remissions, Years
Freund	1908	11
McPhedran	1910	17
Stockton	1919	12
Von Willebrand	1922	10
Speidel and Goss	1924	14
Swan	1925	14-16
Nothmann: Klin. Wchnschr. **8**: 1869, 1929	1929	14
Strandell: Acta med. Scandinav. **72**: 348, 1929	1929	16½
Weber	1932	15
Jenks: J. Iowa M. Soc. **33**: 112, 1943	1943	15

* Partly from Jenks.

MATERIAL

The material here analyzed consists of 54 patients who reentered the hospital because of recurring symptoms of pernicious anemia in relapse some time after a previously diagnosed relapse had been successfully treated with liver. All patients were from an economic level below average and depended in part for subsistence on various forms of financial aid. It is safe to assume that for the most part the diets were suboptimal in animal proteins, the vitamin B factors and vitamin C. The usual method of treatment was to administer approximately 1 unit of liver daily for fifteen days (most patients were used for the purpose of assaying liver) followed by 60 to 90 units per week for the remainder of the patient's stay in the hospital. Patients disappeared from observation at intervals ranging from immediately after discharge from the hospital until forty-five months later. In almost every instance

Aided by a grant from the Wilson Laboratories, Chicago.

From the Hematological Laboratory and the Hektoen Institute for Medical Research of the Cook County Hospital.

1. Osler, William: The Principles and Practice of Medicine, New York, D. Appleton and Co., 1926, p. 747.

2. Cabot, R. C.: Pernicious Anemia—Cryptogenic, in Osler, W., and McCrae, T.: Modern Medicine, Philadelphia, Lea Brothers & Co., 1908, vol. 4, p. 612.

3. Considering the way in which the cases were collected and the difference in diagnostic criteria employed, the authenticity of at least some of these cases may be considered doubtful.

the discontinuance of therapy was voluntary. Usually the patient saw no need for continuing with treatments when he was feeling well, though occasionally the family was unwilling to furnish transportation or assume the financial responsibility when he was considered ineligible for free care. The average amount of liver given during the period of observation varied from 10 to 400 units per month, depending in part on the patient's needs and in part on his regularity of attendance at the outpatient clinic.

TABLE 2.—*Summary of Observations*

	Males	Females
Number of cases	25	29
Number of relapses	48	40
Ages	33 to 73 years	17 to 80 years
Race	Caucasian 24 Chinese 1	Caucasian 25 Negro 4
Time to relapse	3 to 38 months	2 to 30 months
Total relapses per patient	2 to 12	2 to 6
Duration of interval treatment	½ to 37 months	½ to 45 months
Amount of liver given during interval	22 to 2,000 units	25 to 800 units
Red blood cell count at time of relapse	0.64 to 2.36 million	0.43 to 2.60 million

The patients who discontinued therapy returned in relapse at intervals varying from two to thirty-eight months. About 33 per cent relapsed during the first six months, 36 per cent during the next six months, 24 per cent during the second year, 5 per cent during the third year and about 1 per cent later. No arbitrary erythrocyte level was used for the criterion of relapse. In each case the relapse represented an incapacitating illness with levels so low at times as to be barely compatible with life. The highest blood level recorded during relapse was 2.60 million, while the lowest was 0.43 million.

Though multiple relapses were common, 1 case, we believe, was unique (chart 1). In an observation period of ten and one-half years this patient had twelve relapses, the last one, complicated by a fractured femur, resulting in his death.

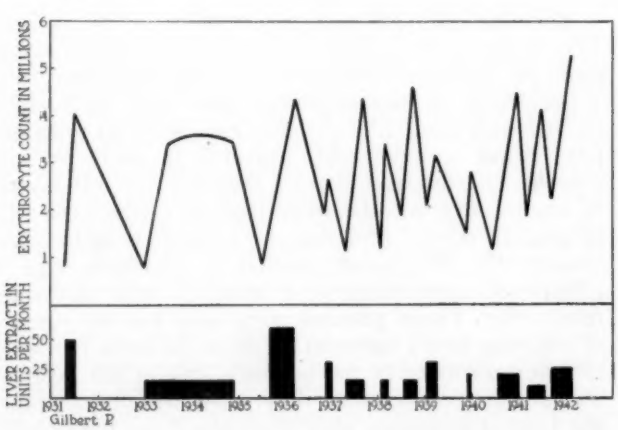

Chart 1.—Patient showing 12 relapses in ten and one-half years due to self neglect.

COMMENT

With the introduction of liver therapy [4] the natural history of pernicious anemia was completely altered. At the time of what usually represented the first relapse an artificial remission was induced by liver, and this remission was maintained by the exhibition of continuous substitution therapy. Occasionally, however, a patient tiring of treatments when feeling well would abandon his treatments, only to relapse at some subsequent date. How long he would maintain himself in the interval without therapy poses a question of great practical importance. Several workers have attempted to investigate the duration of remissions in an attempt to determine what mode of administration of liver might be the method of choice. It would have great practical advantage if, for example, the "depot treatment" was practical. This subject has been investigated by Murray-Lyon,[5] Miller,[6] Strauss and Pohle [7] and Askey,[8] among others. The results of their observations were essentially similar: after the injection of a massive dose of liver extract a more or less complete remission ensues, which lasts from two to twenty-seven months before clinical or hematologic regression again manifests itself. They agree that some storage of the liver principle is possible when massive quantities are injected but that a quantitative storage is unlikely. Nor does there seem to be a relation between the liver requirement (as expressed by the average number of units needed for maintenance therapy) and the "relapse time" following a massive dose. Strauss and Pohle [7] in particular, have pointed out that "patients with pernicious anemia who require relatively little liver extract to maintain a normal blood level may relapse in as short a time as two months after liver therapy is omitted."

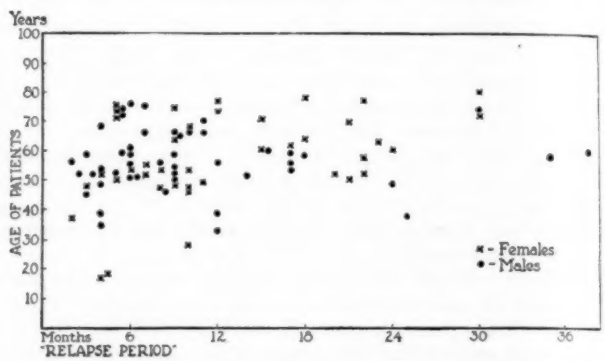

Chart 2.—Lack of correlation between age and sex and the time before relapse after discontinuance of liver therapy.

Although we agree with the fundamentals of the foregoing statements, our observations demonstrate that no conclusions can be drawn from the experiments described, since the factor of relapse is a highly singular phenomenon, which is even remarkably inconstant in the individual patient. Moreover, the arbitrary blood levels assumed by some as representing relapse are also subject to criticism since some patients maintain themselves at suboptimal levels for long periods while others show a continuous decline at a fairly rapid rate.

The individual "relapse period" is probably intimately linked with the quantitative secretion of "intrinsic" factor,[9] the quantity of "extrinsic" and other essential

4. Minot, G. R., and Murphy, W. P.: Treatment of Pernicious Anemia by a Special Diet, J. A. M. A. **87:** 470 (Aug. 14) 1926.

5. Murray-Lyon, R. M.: A Note on the Depot Treatment of Pernicious Anemia, Edinburgh M. J. **43:** 329, 1936.

6. Miller, F. R.: Effect on Pernicious Anemia of Massive Doses of Parenteral Liver Extract, Proc. Soc. Exper. Biol. & Med. **33:** 580, 1936.

7. Strauss, M. B., and Pohle, F. J.: The Duration of Remission in Pernicious Anemia with Liver Therapy, J. A. M. A. **114:** 1318 (April 6) 1940.

8. Askey, J. M.: Quantitative Treatment of Pernicious Anemia, J. A. M. A. **117:** 907 (Sept. 13) 1941.

9. Isaacs, Raphael, and Goldhamer, S. M.: Role of Decreased Amount of Gastric Secretion in Production of Pernicious Anemia, Proc. Soc. Exper. Biol. & Med. **31:** 706, 1933.

dietary factors and the storage of the "anti-pernicious anemia principle" in the liver. That this in itself is not the entire story is proved in part by the fact that no correlation is demonstrable between the "relapse time" and the average amount of liver necessary for maintenance. Some other factor, the nature of which is not at all understood, must be operating in addition. This

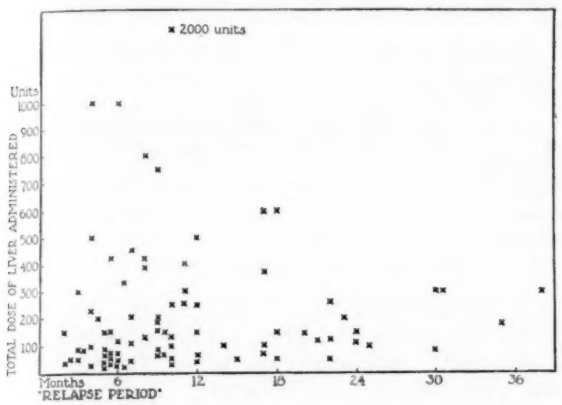

Chart 3.—Absence of demonstrable relationship between total amount of liver administered and time necessary for relapse after discontinuing liver therapy.

is further suggested by the spontaneous and, at least temporarily, complete remissions which have been reported even before liver therapy was discovered. It is conceivable that cyclic changes, changes whose nature or cause is as yet unelucidated, take place in the pyloric gland organ [10] and account for the variability of relapses and individual liver requirement from time to time. Perhaps when these are better understood they will help solve some of the still ill understood problems associated with pernicious anemia.

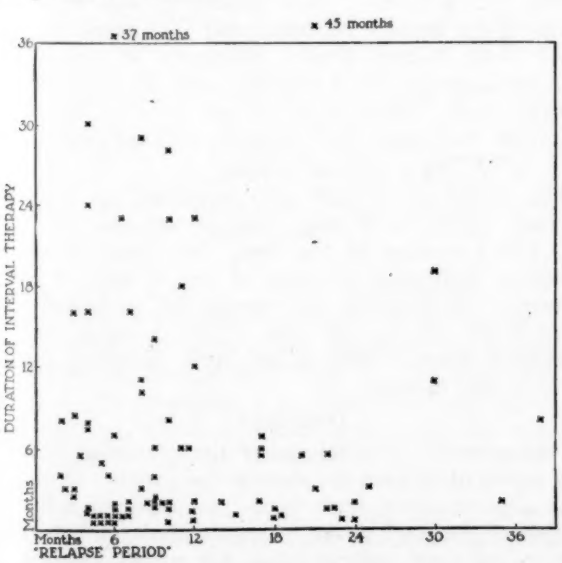

Chart 4.—No difference in time before relapse as related to the length of time liver was administered before its discontinuance.

Attempts to correlate other palpable factors, such as sex, age, race, total amount of liver administered, duration of treatment before discontinuance and average monthly dose, with the "relapse period" were uninformative (charts 2 to 4).

10. Meulengracht, E.: Histologic Investigation into the Pyloric Gland Organ in Pernicious Anemia, Am. J. M. Sc. **197**: 201, 1939.

SUMMARY AND CONCLUSIONS

Fifty-four cases of pernicious anemia in which 88 individual secondary relapses occurred due to self neglect were observed. No correlation could be demonstrated between the age, sex, race, duration of treatment previous to abandonment of therapy, total amount of liver given or average dose and the "relapse period." It is suggested that the amount of "intrinsic factor" secreted, the diet, the storage capacity of the liver and some other as yet unknown factors influence the duration of remissions. It is felt that previous studies attempting to evaluate massive dose therapy and the storage of liver extract were inaccurate because they did not take sufficient cognizance of the highly individualized behavior of patients with pernicious anemia during remissions.

THE DIET AND CHRONIC PEPTIC ULCER

ITS RELATION TO THE COURSE OF THE DISORDER

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WITH THE TECHNICAL ASSISTANCE OF
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In previous studies, lower levels of serum total protein, serum albumin and plasma ascorbic acid were found in patients with chronic peptic ulcer than in comparable persons without clinical evidence of gastrointestinal disorder.[1] Since modification of the chemical structure of blood plasma influences the clinical course of ulcer through its action on motor and secretory functions of the stomach as well as by its effect on healing of the actual ulcer, it seemed of value to determine whether these changes in the blood were an integral part of the disease complex or reflected a deficiency in the diet.

This study presents an analysis of the dietary records of 16 of the group whose blood studies have been reported. These patients, while considered representative of the group as a whole, were selected primarily because of their willingness to cooperate. Their average age was 45, the youngest 21 and the oldest 69. None had suffered any recent exacerbation of ulcer symptoms, and none had been following a prescribed dietary regimen at the time of this study. According to their own statements, no radical change in food habits had occurred during the period of ulcer symptoms; 75 per cent, however, admitted that nausea, postprandial distention or discomfort influenced the amount of food eaten. In common with the entire group under observation, these individuals were underweight. The average weight deficiency amounted to 16 per cent of the ideal weight based on height and age; 4 were less than 10 per cent underweight, 7 more than 20 per cent.

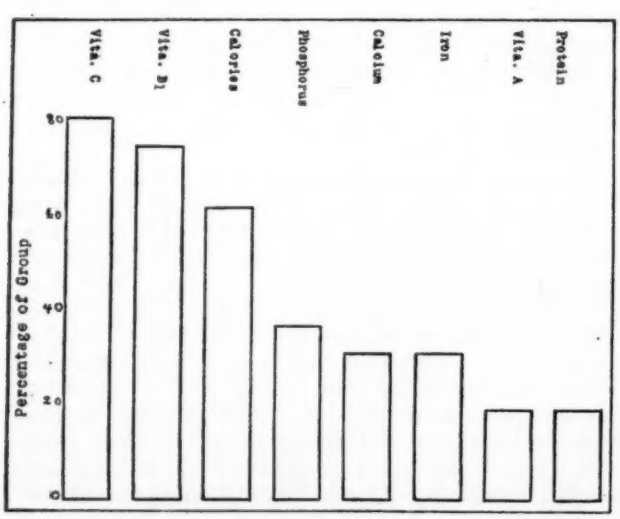
From the Laboratories and Wards of the Philadelphia General Hospital. The work was supported by a grant from John Wyeth and Brother, Inc.
This is the fourth of a series of papers dealing with various aspects of peptic ulcer.

1. Riggs, H. E.; Reinhold, J. G.; Boles, R. S., and Shore, P. S.: Quantitative Circulatory Deficiencies Observed in Peptic Ulcer, Am. J. Digest Dis. **8**: 383-387 (Oct.) 1941.

The patients were sent to a graduate dietitian assigned by the hospital [2] for instruction in compiling dietary records; later the same dietitian reviewed the completed record with the patient. The food diary covered a period of seven days, listing all food eaten during that period together with the amount. From these records the average food intake of the group as well as the nutritional value of the individual diets was computed. The daily allowances for specific nutrients recommended by the Committee on Foods and Nutrition of the National Research Council were used as standards for comparison; [3] daily consumption of less than two thirds of this amount was arbitrarily considered evidence of deficiency. In calculating the vitamin content of the diet, allowance for loss during cooking was estimated by deducting 20 per cent from the vitamin C content of the raw food and 33⅓ per cent from the vitamin B_1 value. When more than one value was recorded for vitamin content of any food, the mean of those given was used.

RESULTS

The diet of the group was found to be low in caloric value and deficient, by the criteria established, in vitamins B_1 and C, as shown in the chart. Owing to wide variations in food intake, greater nutritional deficiencies were present in individual diets than indicated by the mean. The poor caloric intake ($1,718 \pm 600$ calories) was due largely to lack of energy producing foods in the diet. The average diet contained 70 ± 30 Gm. of fat and 205 ± 75 Gm. of carbohydrate, contributing only $1,452 \pm 500$ calories for energy production. The inadequacy of the diets in this respect is emphasized by comparing the value (2,220 calories) allotted to the same classes of foodstuffs in the 2,500 calory diet recommended for persons engaged in sedentary work. Seven (44 per cent) diets contained less fat than the minimum ration (57 Gm.) adopted by the Interallied Food Committee for use during World War I.[4] Eleven (79 per cent) diets included less than two thirds of the amount of carbohydrate customarily allotted (50 per cent total calories = 312 Gm.) to the diet of sedentary workers.



Nutritional deficiencies in peptic ulcer group (intake less than two-thirds recommended daily allowance).

While restriction in food energy value was most outstanding, the average amount of protein (65 ± 26 Gm.) consumed was less than that recommended. Considering the low caloric value of the diets, the ratio of protein food was good (16 per cent), but on the basis of normal weight only five (31 per cent) diets supplied an average of 1 gram per kilogram and three (19 per cent) approached an actual deficiency level of less than 0.7 Gm. per kilogram. High value proteins—milk, eggs, lean meat—made up two thirds of the total protein, but again the actual intake (46 ± 8 Gm.) was below the amount considered adequate to maintain nitrogen equilibrium.[5]

Diet of 16 Patients with Chronic Peptic Ulcer

	Calories	Protein, Gm.	Vitamin A, Units	Vitamin B_1, Units	Vitamin C, Mg.	Calcium, Gm.	Phosphorus, Gm.	Iron, Mg.
Recommended daily intake	2,500	70	5,000	500	75	0.80	1.32	12
Diet, ulcer patients	$1,718 \pm 600$	65 ± 26	$5,800 \pm 2,660$	265 ± 100	34 ± 17	0.98 ± 0.7	1.21 ± 0.6	10 ± 3

The relatively high ratio of protein in the diet was in large measure due to heavy consumption of milk. As a result the vitamin A content ($5,800 \pm 2,663$ international units) was above the recommended level. In three diets, however, the content of this vitamin was low enough to be considered inadequate. In contrast to vitamin A, the diet was extremely poor in thiamine and ascorbic acid. The average level of vitamin B_1 was 265 ± 100 international units, with twelve (75 per cent) diets containing less than two thirds of the amount recommended. Thirteen (81 per cent) diets showed similar deficiency in vitamin C, with the average diet containing only 34 ± 17 mg. of ascorbic acid. More than 25 per cent of the diets contained less than the estimated maintenance allowance (25-30 mg.) of this vitamin.[6]

The liberal use of milk also accounted for the high calcium (0.98 ± 0.70 mg.) and phosphorus (1.21 ± 0.60 Gm.) content of the diet: Six diets, however, contained inadequate amounts of one or both of these elements. By contrast, the average diet contained only a minimum amount of iron (10 ± 3 mg.), and 5 patients consumed diets which were definitely inadequate in this mineral.

COMMENT

Poor selection of food rather than financial restriction appeared to limit the diet of this group. Proteins, especially the costly, high value type, made up a liberal portion of the food intake. Despite its large contribution to the total caloric value, the actual amount of protein consumed was not sufficient to supply tissue requirements and to substitute for fat and carbohydrate as a source of energy. Failure to include adequate fruit and vegetables in the diet was one of the causes of its low caloric value as well as of its deficiency in vitamin C. This class of foodstuffs contributed less

2. Miss Elizabeth Miller, chief dietitian of the Philadelphia General Hospital, provided this assistance.

3. The level for phosphorus in the diet (1.32 Gm.) is that recommended by Stiebeling and Phipard.[6]

4. Wright, Samson: Applied Physiology, ed. 6, London, Oxford University Press, 1937.

5. Everett, M. R.: Medical Biochemistry, New York, Paul B. Hoeber, Inc., 1942.

6. Stiebeling, H. K., and Phipard, E. F.: Diets of Families of Employed Wage Earners and Clerical Workers in Cities, Circular 507, United States Department of Agriculture, January 1939.

than 10 per cent of the total calories and provided only 34 Gm. of carbohydrate. As a source of thiamine it contributed only 0.17 mg. (58 international units). Fruits and succulent vegetables, especially of the leafy types, rarely appeared on these diet lists. Citrus fruits or tomatoes in any form contributed only 8 mg. of ascorbic acid and were absent in over 65 per cent of the individual diets. Omission of fruit and vegetables was not entirely attributable to seasonal trends, although the records were compiled in winter and early spring. During the same period, diets of a comparable group without gastrointestinal disorder showed an ascorbic acid content of 75 ± 33 mg.

In some respects the large consumption of milk compensated for the absence of fruit and vegetables. This foodstuff provided 29 per cent of the caloric intake as well as 35 per cent of the dietary protein, 41 per cent of the vitamin A content and 31 per cent of the thiamine. Milk also added greatly to the mineral content, providing half of the phosphorus and three fourths of the calcium. Since most of the calcium (90 per cent) was obtained from sources also rich in phosphorus and little from vegetables and fruit which are relatively low in phosphorus, the normal ratio of these two minerals in the diet was reversed (0.8), with 81 per cent of the diets containing a calcium-phosphorus ratio less than 1. Under these conditions, inadequate retention of both minerals may have resulted, in spite of the liberal dietary supplies.

The deficiencies in diet brought out by these studies are an argument for relating alterations in composition of the blood to inadequate food intake. Diet, however, may not be the only factor determining the nutritional status of these persons. Alterations in digestion and absorption resulting from the gastrointestinal lesion may also influence nutrition, even with an adequate, balanced food intake, and must certainly amplify deficiencies in diet. That this factor must be considered in evaluating the nutrition of patients with chronic ulcer was demonstrated by comparing levels of blood ascorbic acid with dietary content of the same vitamin. Close correlation (coefficient of correlation $= 0.8$) was present in the group without gastrointestinal disorders, but no similar relationship (coefficient of correlation $= 0.3$) could be established for the patients with ulcer.

In addition to the physiologic effects mediated through the changes in blood composition, some of the clinical features associated with the chronic ulcer syndrome may be more closely allied to the dietary deficiencies of the patient than to the gastrointestinal lesion. Constipation may reflect the lack of bulk in the diet or, when associated with distention, the effect of thiamine lack on intestinal tonus. Thiamine deficiency, originating through the voluntary restriction of diet by patients with chronic ulcer, may defeat efforts to improve nutrition and tend to perpetuate itself by causing anorexia and nausea.

SUMMARY

The diets of 16 patients with chronic peptic ulcer were found to be poorly balanced and deficient in food energy value as well as in thiamine and ascorbic acid.

It is suggested that alterations in the composition of the blood found in these patients as well as some of the clinical symptoms may be related to the inadequate diet.

THE TREATMENT OF INTRACRANIAL INFECTIONS WITH PENICILLIN

REPORT OF THREE CASES

CAPTAIN ALBERT L. EVANS
MEDICAL CORPS, ARMY OF THE UNITED STATES

Penicillin, the powerful antibacterial agent produced by growth of the fungus Penicillium notatum, has been used with dramatic results in cases of infections heretofore usually fatal to man. Until the advent of the sulfonamides it was rare for persons with pneumococcic or staphylococcic meningitis to survive. Reports of such survivals have appeared in the literature more frequently since these agents have been used, but penicillin seems to offer more hope for cure of these maladies than any other substance known at the present time. Two cases of staphylococcic meningitis and 1 case of pneumococcic meningitis are herewith reported as having been cured with penicillin at Lawson General Hospital. It is felt that survival would not have occurred with the types of therapy in practice prior to the advent of penicillin.

REPORT OF CASES

CASE 1.—*Pneumococcic (type 18) meningitis.* A white man aged 35, admitted to the hospital on Aug. 22, 1943, had sustained a compound fracture of the skull, left frontal area and cribriform plate on July 8, when a swamp glider overturned and the propeller struck his head. He was admitted to his station hospital in an unconscious state. The wound was debrided. He was treated for fracture of the skull and cerebral contusion and was hospitalized for a month. It was noted that he had a cerebrospinal fluid rhinorrhea. He was transferred to his quarters on August 10, and the rhinorrhea stopped on his twelfth day in quarters, August 21. Severe headache, nausea, vomiting and typical signs of a virulent meningitis then developed. He was flown to Lawson General Hospital and admitted three days after the onset of signs of meningitis. X-ray examination of the skull revealed a subdural pneumocephalus of the left frontal area. Examination of the spinal fluid revealed the offending organism to be a type 18 pneumococcus. This apparently had invaded the meninges through the fracture of the frontal sinus and cribriform plate. Pneumococci were so numerous in the spinal fluid that the organisms could be seen while one was counting the cells. He was given an initial dose of penicillin of 30,000 units intravenously, followed by 5,000 units intravenously at thirty minute intervals for eight doses. He was then given 20,000 units intramuscularly every three hours for ten days. This was supplemented by intrathecal administration of 5,000 units every twenty-four hours for twelve days. The first five injections were made into the cisterna magna and the injections thereafter into the dural sac at the third lumbar interspace. An immediate response was obtained in the culture of the spinal fluid as well as in the cell count, and after twenty-four hours culture and smear were negative. At no time was there evidence of additional irritation to the cord or meninges following the intrathecal use of penicillin. On the fifth day of treatment the patient became dull and lethargic. Another roentgenogram of his skull was made, which showed a fluid level in the pneumocephalus of the frontal region. A burr hole craniotomy was performed and the air removed. Pus was not found in this region, but 5,000 units of penicillin was inserted directly into the cavity at the time of operation. The patient was supported with blood transfusions and his fluid balance maintained with intravenous fluids. His improvement was progressive, and he made an uneventful recovery, with no demonstrable residuals at the present time. He received a total of 2,085,000 units of penicillin.

It may be added that this patient received 6 Gm. of sulfathiazole by mouth at his station hospital and 12.5 Gm. of

sodium sulfadiazine intravenously at Lawson General Hospital prior to the institution of penicillin therapy. The fact that a profuse growth of pneumococci was still present suggests resistance of the organisms to the sulfonamides.

CASE 2.—*Abscess of the brain with meningitis.* A white man aged 22, admitted to the hospital on June 24, 1943, had had an infection of the upper respiratory tract for four days. Three days before his admission he had fallen from his bed, striking his forehead. He had not been unconscious, but he complained of severe headache and pronounced nasal congestion. Examination by the otorhinolaryngologist revealed considerable pus coming from the right middle meatus. The right eye became noticeably swollen and there was tenderness over the right frontal sinus. X-ray examination showed no evidence of fracture of the right frontal bone. The patient appeared to be acutely ill. His temperature was 103.6 F. A diagnosis of frontal sinusitis was made, and use of sulfadiazine was started. On the following day stiffness of the neck and pain on flexion were first noted and meningitis was suspected. A lumbar puncture was done, which showed an initial pressure of 275 mm. of water. The fluid was clear but contained 52 cells, of which 75 per cent were polymorphonuclear leukocytes. No organisms were found on smear or by culture. The possibility of an infection of the blood stream and a thrombophlebitis of the ophthalmic vein was considered. The blood sulfadiazine level of 7.7 mm. was felt to be inadequate, and the dosage was increased. The disease ran an afebrile course, and the patient's general condition improved, as did the swelling about the eye.

On July 5 a spinal tap was performed and 15 cc. of clear fluid was removed. The initial pressure was then 170 mm. of water. Examination of the fluid showed 5 cells, 3 of which were polymorphonuclear leukocytes. The temperature later became elevated, and at noon the next day the patient was disoriented but not comatose. He had a weakness of the left side of the face and weakness of the entire left side of a minimal degree. A diagnosis of abscess of the brain in the region of the right frontal lobe was made. With the area under procaine hydrochloride anesthesia a burr hole was made in the right frontal region. The brain was found to be under considerable tension. A needle directed toward the frontal horn of the ventricle encountered a mixture of ventricular fluid and pus. A small amount of air was allowed to enter the needle. Two cc. of iodized poppy seed oil was injected to outline the limits of the cavity. Roentgenograms made after this procedure revealed that the abscess cavity had ruptured into the ventricle. Progressive signs of meningitis rapidly developed. The ventricle was tapped daily through the burr hole and found on each occasion to contain a seropurulent fluid from which Staphylococcus aureus was grown. By the fifth postoperative day the fluid was less turbid, and aspiration was stopped on the seventh postoperative day. By July 24 the stiffness of the neck had almost subsided, the temperature and pulse had returned to normal and there was relatively little difference in the strength of the upper extremities. By July 29 the rigidity of the neck and spine had entirely disappeared. On August 4 because of nausea and vomiting, the use of sulfadiazine was discontinued. The course was uneventful for approximately one month, but on the morning of September 5 the patient complained of vertigo and drowsiness, symptoms which became more severe. On September 8 a ventriculogram was made; it gave evidence of a mass in the right frontal region. A right craniotomy was performed. An abscess was evacuated and a catheter inserted into the cavity. Through this catheter penicillin was administered daily for seven days. Penicillin was also administered systemically—an initial dose of 30,000 units intravenously followed by 5,000 units intravenously every thirty minutes for six doses. He was then given intramuscular injections of 20,000 units every three hours. His condition initially improved, but on the fourth day of treatment clinical signs of meningitis developed. Lumbar puncture revealed a grossly turbid fluid with 4,100 leukocytes, 95 per cent of which were polymorphonuclears. Intrathecal administration of 5,000 units of penicillin by the lumbar route was instituted, and injections were repeated every twenty-four hours for nine days. Repeated cultures and smears of the spinal fluid failed to reveal organisms. It is felt that since the patient had received 420,200 units of penicillin prior to the appearance of meningeal signs the exudate had been sterilized of Staph. aureus, which caused a nonspecific meningitis. Penicillin therapy was maintained for twelve days, during which time he received 1,793,700 units. He made a progressive and uneventful recovery and was discharged on November 20 after six weeks' observation showed no evidence of recurrence of infection or neurologic residuals.

CASE 3.—*Staphylococcic meningitis.* A white man aged 26, admitted to the hospital on Aug. 31, 1943, had experienced intermittent dull pain and slight stiffness of the cervical region since January 1941, when he sustained an injury to his neck while playing basketball. In March 1943 he first noticed lameness of the right lower extremity on saluting and shaving. In June 1943 muscular twitchings of the right extremities accompanied by some paresthesia developed. He was unable to perform rapid movements with the right arm or leg. He was admitted to the hospital, where examination revealed weakness of all muscles of the right upper extremity and of the right hamstring group. Reflexes were exaggerated bilaterally but more so on the right side. Spinal puncture revealed a pronounced increase in protein (2,680 mg. per hundred cubic centimeters), and a Queckenstedt test gave evidence of a fluid block. He was transferred to Lawson General Hospital, where on September 6 a pantopaque myelogram of the cervical region showed a definite space-displacing mass in the cervical region. On September 7 a cervical laminectomy was performed, and a large tumor was located, extending from the foramen magnum down to the sixth cervical vertebra and possibly further. It filled the entire canal and appeared to be intramedullary. The greater portion seemed to be to the right of the midline, and its appearance suggested a hemangioma. The immediate postoperative course was uneventful. A total dose of 2,000 roentgens was given over a period of ten days. The patient made clinical improvement. On October 1 a cystic swelling was noted at the operative site, and 30 cc. of bloody spinal fluid, from which Staphylococcus albus was cultured, was aspirated from this area. On October 7 clinical signs of meningitis developed, and the patient rapidly became acutely ill. Penicillin therapy was instituted with injection of 20,000 units intramuscularly every three hours. Twenty thousand units was injected into the cervical region. The following day the dosage of penicillin was increased to 25,000 units intramuscularly every three hours. Daily cervical and lumbar injections of 5,000 units were administered for four days. Because of block in spinal canal there was little absorption of the penicillin in the lumbar region, and the yellow pigment of the drug was seen at each puncture. The fluid from both areas was bacteriologically negative after twenty-four hours of penicillin therapy, but the leukocyte count remained elevated for eight days. The patient made definite improvement, but because of his poor condition it was decided to aspirate as much of the fluid as possible through the cervical region and replace it with penicillin solution (500 units per cubic centimeter). Therefore 25,000 units penicillin was introduced after the aspiration of 100 to 150 cc. of fluid, without ill effect, for six days. He made progressive improvement. Treatment was continued for ten days, during which time he received a total of 1,470,000 units. The spinal fluid was clear and the cultures negative. He has shown no evidence of recurrence of meningitis.

COMMENT

Rammelkamp and Keefer [1] have shown that penicillin is not detectable in the spinal fluid after systemic administration. Pilcher and Meacham [2] showed that for experimental animals intrathecal penicillin therapy was of value in the treatment of staphylococcic meningitis but intravenous therapy was of little if any benefit.

1. Rammelkamp, C. H. and Keefer, C. S.: The Absorption, Excretion and Distribution of Penicillin, J. Clin. Investigation **22**: 425 (May) 1943.
2. Pilcher, Cobb, and Meacham, William F.: The Chemotherapy of Intracranial Infections: III. The Treatment of Experimental Staphylococcic Meningitis with Intrathecal Administration of Penicillin, J. A. M. A. **123**: 330 (Oct. 9) 1943.

The patients at Lawson General Hospital were so seriously ill that penicillin was given both intrathecally and systemically in order to give them the benefit of all forms of therapy.

Intrathecal use of penicillin in large concentrations has been shown by Rammelkamp and Keefer [3] to produce a pleocytosis in the cerebrospinal fluid but no other significant toxic effect in man. This has been verified in experimental animals by Pilcher and Meacham.[2] It is interesting to note that in case 3 25,000 units was administered by the intrathecal route without producing a pleocytosis or other toxic manifestations. The cell count of the spinal fluid became progressively lower, even with concentrations of 25,000 units at twenty-four hour intervals.

SUMMARY

1. In 3 cases of meningitis, 2 staphylococcic and 1 pneumococcic, cures were obtained, for which penicillin is given the major credit.

2. Intrathecal administration of penicillin in cases of meningitis is thought to be of great value.

3. Penicillin is a valuable addition to the medical armamentarium for the treatment of intracranial infections due to the staphlococci and pneumococci.

Clinical Notes, Suggestions and New Instruments

AMEBIC ABSCESS OF THE LIVER WITH SECONDARY INFECTION

LOCAL TREATMENT WITH PENICILLIN

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DETROIT

Amebic abscesses of the liver may be divided into two groups from the standpoints of therapy and prognosis. The first group is composed of those without secondary bacterial infection. The accepted method of therapy in this group is the administration of emetine hydrochloride, usually combined with aspiration of the abscess. Open drainage is contraindicated, since it causes a higher fatality rate, chiefly because of the unavoidable postoperative bacterial invasion of the abscess. In a collected series of 5,000 cases, Ochsner and DeBakey [1] report a fatality rate of 5.6 per cent for the cases treated by the closed method and 43.1 per cent for the cases treated by open drainage.

The second group consists of amebic abscesses which have become secondarily infected with bacteria of various types. In these cases the prognosis is much worse, and the accepted surgical treatment is essentially the same as for other pyogenic hepatic abscesses, namely open drainage performed preferably through an extraserous approach. Because of the higher fatality rates associated with open drainage, it has been suggested that some of these infected abscesses might possibly respond to aspiration combined with sulfonamide therapy. Alport and Ghalioungui [2] report a case of what was presumably an amebic abscess of the liver secondarily infected by Bacillus pyocyaneus in which recovery followed repeated aspirations and the local and systemic use of some of the earlier sulfonamide compounds.

The chief point of interest in the present case is the use of penicillin injected into the cavity of an amebic abscess of the liver secondarily infected with beta-hemolytic streptococci of Lancefield group G.

REPORT OF CASE

History.—A Negro aged 41 was admitted to Detroit Receiving Hospital on April 22, 1943 complaining of sharp interscapular pain of twenty-four hours' duration.

The patient had been in good health until the first week of December 1942, when he contracted a "head cold." About one week later he began to cough and noticed a sharp stabbing pain in the lower right side of his chest. He consulted a physician, who told him that he had pleurisy and advised him to stay in bed. The pain became less sharp but persisted as a steady dull ache, which extended downward over the right upper abdominal quadrant. The cough also persisted and was productive of white odorless sputum. During the succeeding months the patient remained ill, confined to his home, and spent most of the time in bed. There was a gradual loss of 18 to 20 pounds (8 to 9 Kg.), mild anorexia, gaseousness and infrequent periods of slight diarrhea alternating with constipation. His general condition improved somewhat by the first of April, and he considered returning to work. His physician advised him, however, to remain at home. About April 15 he began to have night sweats but was unaware of fever or chills. On April 21 a sharp stabbing pain developed in the interscapular area. It was intensified by muscular movements but was not influenced by respiration.

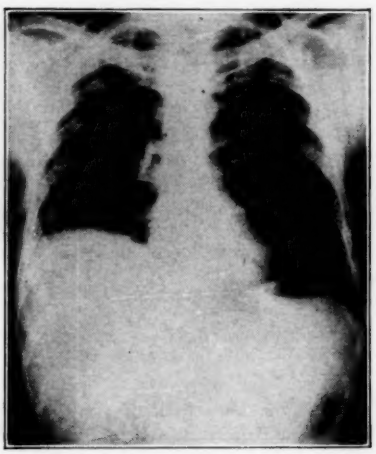

Fig. 1.—Appearance of the chest on Dec. 10, 1938. Note the elevation of the right side of the diaphragm. Compare with figure 2 *A*.

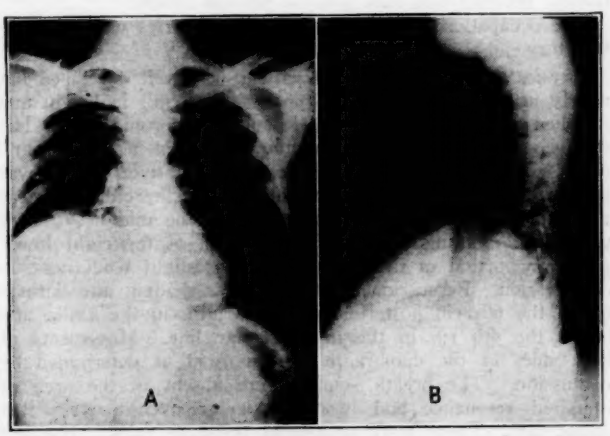

Fig. 2.—Appearance of the chest on May 15, 1943. *A*, anteroposterior and *B*, lateral views showing elevation of the right side of the diaphragm.

His general health had been good. In 1921 he noticed a sore on his penis but received no treatment for it. In 1926 he was treated for gonorrhea.

In 1938 he was sent to Parkside Hospital in Detroit because his physician suspected that he was suffering from pneumonia. Review of the hospital records reveals that he complained chiefly of pain in his back and in the right side of his chest and abdomen. He had no cough, and the pain in his chest was not pleuritic in type. There were no gastrointestinal

3. Rammelkamp, C. H., and Keefer, C. S.: The Absorption, Excretion and Toxicity of Penicillin Administered by Intrathecal Injection, Am. J. M. Sc. **205**: 342 (March) 1943.

From the Departments of Medicine and Surgery of Wayne University College of Medicine and City of Detroit Receiving Hospital.

1. Ochsner, A., and DeBakey, M.: Amebic Hepatitis and Hepatic Abscess, Surgery **13**: 460-493 (March); 612-649 (April) 1943.

2. Alport, A. C., and Ghalioungui, P.: Conservative Treatment of Liver Abscesses, Lancet **2**: 1062-1065 (Nov. 18) 1939.

complaints. Physical examination of the chest showed only an elevation of the right side of the diaphragm. Except for slight tenderness in the right lumbar region, there were no abnormal abdominal findings. The Kahn reaction of the blood was strongly positive. A roentgenogram of the chest (fig. 1) showed the lungs to be clear, but the dome of the right side of the diaphragm was at the level of the fourth interspace anteriorly. There were no clinical or roentgen findings of atelectasis. The patient's temperature ranged between 98 and

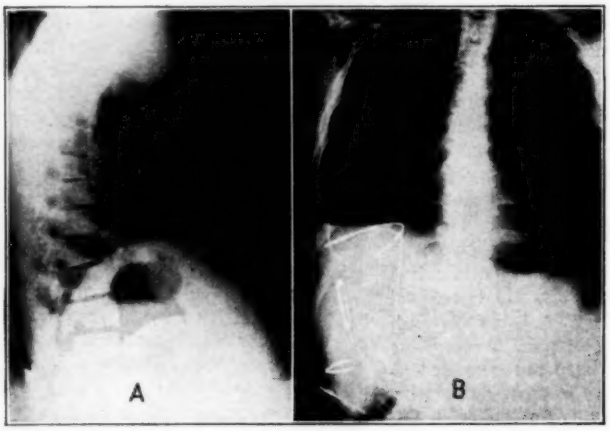

Fig. 3.—*A*, lateral view on May 22, 1943, showing the elevated diaphragm and the abscess cavity in the liver. *B*, anteroposterior view on June 4, showing the ureteral catheter coiled within the abscess cavity.

103 F. during the first eight days, then diminished, and was normal after the twelfth day. The tentative diagnosis was syphilis of the liver. The patient received several injections of a bismuth compound but did not recall having taken any antisyphilitic treatment after leaving the hospital.

In 1940 he was caught between a truck and a coal conveyor and was told that he had sustained an injury of the liver. He was brought to Redford Receiving Hospital, where he remained only overnight. A roentgenogram of the chest showed no fractures of the ribs and the diaphragm in a normal position. His past history by systems was essentially negative except for a three day period of diarrhea in 1939, which he attributed to food eaten in a restaurant. His bowel habits had been normal between that time and the present illness.

The occupational, marital and family histories were noncontributory.

Physical Examination.—The patient was well developed but poorly nourished, was 5 feet 7 inches (170 cm.) in height and weighed 110 pounds (50 Kg.). He appeared chronically ill. His mental state was clear. Examination of the skin, head, eyes, ears, nose, mouth, and throat was essentially negative. There was no cervical or other lymphadenopathy. The thyroid gland was of normal size, and the trachea was in the midline. There were some bulging and lag in expansion of the right lower posterior portion of the thorax but only slight tenderness on compression. Percussion revealed dulness shading into flatness below the 6th rib posteriorly on the right, in the axilla and below the 4th rib in the midclavicular line. Movements of both sides of the diaphragm were normal as determined by percussion. The breath sounds were absent in the area of impaired resonance and bronchovesicular over a strip just above this. There were occasional crepitant rales. The left lung was clear. The cardiac apical impulse was located in the fifth intercostal space 9 cm. to the left of the midsternal line. Percussion borders were normal. There were no murmurs. The blood pressure was 125/85. Examination of the abdomen revealed tenderness and voluntary muscular rigidity in the right upper quadrant, with an ill defined underlying mass. Evidences of ascites were absent. Rectal examination showed no abnormalities other than a slight enlargement of the prostate gland. The genitalia and the extremities showed nothing remarkable.

Initial Laboratory Studies.—Urinalysis revealed a specific gravity of 1.018, a trace of albumin, no sugar, and 75 leukocytes in each high power field of the centrifuged specimen. The blood contained 3.64 million erythrocytes, and the value for hemoglobin was 5.7 Gm. There were 23,100 leukocytes with the following differential count: neutrophils 74 per cent, of which 46 were filamented and 28 nonfilamented forms; lymphocytes 24 per cent; monocytes 2 per cent. The icterus index was 5.0 and the blood urea 26 mg. per hundred cubic centimeters. The Kline reaction of the blood was negative, as was the blood culture. The value for serum albumin was 2.2 Gm. and that for serum globulin 5.1 Gm. per hundred cubic centimeters. Ingestion of 6.0 Gm. of sodium benzoate resulted in the excretion of only 0.72 Gm. of hippuric acid (expressed as sodium benzoate) in the urine during a period of four hours. The stool was described as soft and brown and gave a strongly positive reaction for occult blood. The sputum contained no tubercle bacilli on repeated tests.

Clinical Course.—During the first three weeks the patient's temperature varied between 99 and 101 F., with a corresponding elevation in pulse rate. He did not appear acutely ill. However, diarrhea became more pronounced than at any previous time, consisting of two to four soft, unformed, brown stools daily. The abdominal tenderness gradually subsided, and the edge of the liver could be defined about 10 centimeters below the right costal margin. Roentgenograms showed elevation of the right side of the diaphragm (fig. 2*A* and *B*). Fluoroscopy revealed normal motion of both sides of the diaphragm.

The combined physical and roentgen findings suggested the diagnosis of hepatic abscess. Stool examinations for parasites were ordered because amebiasis was suspected. After three negative tests, trophozoites of Endamoeba histolytica were found on May 12 and again on May 13. On the latter date and for the ten following days 1 grain (0.06 Gm.) of emetine hydrochloride was injected subcutaneously each day. Additional treatment for the severe diffuse hepatic damage included a diet high in carbohydrate and protein and low in fat and containing generous amounts of brewers' yeast, thiamine hydrochloride, nicotinic acid, halibut liver oil and ascorbic acid. The patient was also given intravenous infusions of dextrose. After three days of this therapy the diarrhea stopped and the thoracic pain disappeared. The patient's temperature decreased to between 99 and 100 F. and his appetite improved. However, serial roentgenograms showed no change in the size of the liver, and the hippuric acid test on May 18 was unchanged.

On May 22 the abscess was aspirated. Procaine hydrochloride was injected into the skin and subcutaneous tissues at the right costal margin in the midclavicular line. A small incision was made in the skin and a 13 gage needle inserted. It was directed upward and posteriorly for a distance of about 4 inches. At this point considerable resistance was encountered. Additional pressure, however, sufficed to force the needle into the abscess cavity, from which 350 cc. of thick gray pus was obtained. Smears showed no amebas but many leukocytes and streptococci, both graded quantitatively as 4+. When grown on blood agar the streptococcus exhibited beta hemolysis. Serologic grouping [3] revealed that it belonged to group G of Lancefield. Figure 3*A* is a lateral view taken just after aspiration of the abscess cavity.

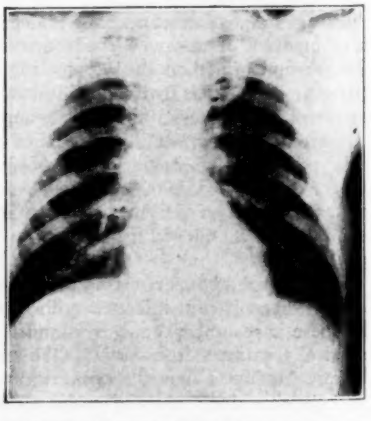

Fig. 4.—Appearance of the chest on September 13, showing the return of the right side of the diaphragm to its normal position.

3. The serologic grouping of the hemolytic streptococcus was done by Miss Miriam Miller under the direction of Dr. Ivan C. Hall in the Central Laboratory of the Contaminated Wound Project of the Subcommittee on Surgical Infections of the National Research Council, financed by a contract between the Office of Scientific Research and Development and Columbia University.

Because of the evidence of pronounced hepatic damage which would have made open drainage most hazardous, we decided to inject penicillin [4] into the cavity of the abscess. To accomplish this a 13 gage needle was reinserted and a small ureteral catheter passed through the needle. Then the needle was withdrawn and the catheter left in place. A roentgenogram was taken to check the position of the catheter (fig. 3*B*). Five cc. of isotonic solution of sodium chloride, each containing 5,000 Oxford units of penicillin, was injected into the abscess on the evening of May 22. This process was repeated every four hours until eight doses had been given. The amount of penicillin was then reduced to 10,000 units every four hours. This schedule was maintained for seven days, when the dose was further decreased to 5,000 units every four hours. Seven days later, on June 9, penicillin treatment was stopped. The patient received a total of 830,000 Oxford units during a period of fifteen and one-half days.

On May 25, three days after penicillin was started, a smear of the aspirated material showed leukocytes graded as 4+ but no organisms. Cultures yielded no growth. Subsequent cultures on May 27, May 28, June 2 and June 4 were likewise sterile.

Following aspiration of the abscess and treatment with penicillin the patient became afebrile and asymptomatic. On May 27 the value for the hippuric acid test increased slightly to 0.976 Gm., and the levels for serum albumin and globulin increased to 2.8 and 5.46 Gm. per hundred cubic centimeters respectively. The liver gradually decreased in size, as noted on roentgenographic and physical examination. Except to obtain small amounts of pus for cultures, no further aspirations of the abscess were necessary. Motile amebas reappeared in the stools on July 1. Accordingly, 1 grain of emetine hydrochloride was again given subcutaneously each day for five days and was followed by the oral administration of 12 grains (0.8 Gm.) of chiniofon three times daily for twelve days. At the end of this therapy no amebas were found in the stools, but another specimen on July 22 contained an occasional cyst. Sigmoidoscopy revealed no ulceration of the rectum or of the sigmoid portion of the colon. About this time also the level of serum albumin had increased to 3.5 Gm., while that of globulin had decreased to 3.7 Gm. The value for the hippuric acid test had increased to 1.3 Gm., the erythrocytes to 4,190,000 and the hemoglobin to 10.5 Gm. The patient had gained 29 pounds (13 Kg.).

He was discharged from the hospital on July 26 and has been followed in the outpatient department. He has continued on his diet with its vitamin supplements and recently has been taking vioform. On September 15 examination of the chest was entirely negative, but the edge of the liver, which felt slightly firm, was palpable 5 cm. below the right costal margin. The spleen was not palpable. The value for the hippuric acid test had dropped to 0.707 Gm. The serum albumin and globulin levels were each 3.7 Gm., and the bromsulphalein test following intravenous injection of 5 mg. of the dye for each kilogram of body weight showed 60 per cent retention at 5 minutes, a trace at ½ hour and no retention at 60 minutes. Anteroposterior and lateral roentgenograms of the chest were within normal limits (fig. 4).

COMMENT

This case illustrates the value of roentgenography in the diagnosis of amebic abscess of the liver. The patient's chief complaints were related to the thorax, and the history of occasional periods of diarrhea was obtained only after repeated questionings. The physical findings on admission were equivocal, and if it had not been for the roentgenogram which clearly localized the disease of the liver there might have been delay in arriving at the correct diagnosis. The roentgenograms (fig. 2*A* and *B*) are very similar to those published by Ochsner and DeBakey [1] except that in our case the typical obliteration of the anterior costophrenic angle was absent. Furthermore, the diaphragmatic movements as observed fluoroscopically were not noticeably decreased. The latter finding seemed to favor the diagnosis of hepatic abscess rather than an abscess in the subdiaphragmatic space, which would certainly have immobilized the diaphragm. However, it is reported that diaphragmatic movement is frequently impaired in amebic abscesses of the liver. It is noteworthy that in Ochsner and DeBakey's [1] cases a correct roentgenographic diagnosis was made in 88 per cent.

Another remarkable feature of this case is the clinical and roentgenographic evidence that, in all probability, an amebic infection of the liver was present in December 1938, four years preceding the onset of the symptoms of the present illness. This process, whether a diffuse amebic hepatitis or an actual amebic abscess, had at least partially subsided, as shown by the normal position of the diaphragm in the roentgenogram taken in 1940. If this was the actual course of events, the duration of the disease was unusually long, for among 113 cases classified by Ochsner and DeBakey as chronic amebic abscesses the average duration of symptoms was three to six months and the longest duration three years.

The final point of interest is the consideration of the value of penicillin therapy in this case and its possible value in other cases of secondarily infected amebic abscesses of the liver. The high fatality rate usually associated with open drainage has been mentioned. It should be stated, however, that Ochsner and DeBakey [1] succeeded in reducing this fatality rate to only 6.6 per cent in a group of 15 cases in which extraserous drainage was employed. Even this figure could perhaps be further reduced if operation could be avoided. The use of sulfonamide compounds in 1 reported case also has been mentioned. One might predict that, while sulfonamide therapy would tend to prevent the spread of secondary pyogenic infection throughout the liver, it would not be expected to sterilize the abscess itself, since its action, as in empyema thoracis, is greatly interfered with by the presence of pus. The action of penicillin, on the other hand, is not altered by the presence of pus,[5] as indicated by experimental evidences and its successful clinical use in empyema thoracis and other deep suppurative processes. Therefore one might expect that it would have a favorable effect, particularly when used locally.

It is impossible to judge the value of penicillin in the treatment of secondarily infected amebic abscesses of the liver merely from the results in this 1 case. The practically complete absence of fever or symptoms after a few days of therapy with emetine would seem to indicate that either the streptococcus was of low virulence or that the thick abscess wall minimized the systemic reaction to the infection. However, the organisms were present in very large numbers. While most severe infections in human beings due to beta-hemolytic streptococci are caused by group A organisms, other Lancefield groups may cause infections at times.

Group G beta-hemolytic streptococci were at first thought to be rarely if ever associated with severe human infections,[6] but more recently they have been reported as the causative organisms in such diseases as recurrent lymphangitis and septicemia,[7] puerperal fever with and without septicemia,[8] fatal acute bacterial endocarditis [9] and 2 cases of subacute bacterial

4. The penicillin was made available by Dr. Chester S. Keefer, consultant to the Committee on Medical Research, under a contract between the Office of Scientific Research and Development and the Massachusetts Memorial Hospitals.

5. Abraham, E. P., and others: Further Observations on Penicillin, Lancet **2**: 177-188 (Aug. 16) 1941.

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7. Morales Otero, P., and Pomales Lebron, A.: Grouping of Hemolytic Streptococci Isolated in Puerto Rico, Proc. Soc. Exper. Biol. & Med. **34**: 105 (Feb.) 1936.

8. Colebrook, L., and Purdie, A. W.: Treatment of 106 Cases of Puerperal Fever by Sulfanilamide, Lancet **2**: 1237-1242 (Nov. 27) 1937. Ramsay, A. M., and Gillespie, M.: Puerperal Infection Associated with Hemolytic Streptococci Other Than Lancefield's Group A, J. Obst. & Gynaec. Brit. Emp. **48**: 569-585 (Oct.) 1941.

9. MacDonald, I.: Fatal and Severe Human Infections with Hemolytic Streptococci Group G (Lancefield), M. J. Australia **2**: 471-475 (Sept. 23) 1939.

endocarditis.[10] They have been isolated also from the human respiratory tract[11] and other human clinical sources,[12] including the feces. In many of the latter sources they have produced only mild infections or were not pathogenic at all. In the present case penicillin caused the rapid destruction of these streptococci, whatever their effect might have been on the clinical outcome.

A trial of aspiration combined with injections of penicillin for the purpose of avoiding open drainage would seem to be desirable in other cases of this kind. Recent studies[13] indicate that the dosage of penicillin used in this case was probably unnecessarily large. Thus in the treatment of empyema thoracis it is recommended that 30,000 or 40,000 units be injected once or twice daily. It is probable also that, while in the present case it seemed unnecessary to aspirate material from the abscess cavity repeatedly, other cases might be benefited by this additional procedure. Such aspirations should not be repeated too frequently, however, since it requires at least six or eight hours for penicillin to exert its maximum effect. For the same reason the use of penicillin as an irrigating solution would be illogical.

The results in this case have been encouraging. It is hoped that those who have similar cases will employ this method of treatment in order to determine whether it will be possible to avoid open drainage in secondarily infected amebic abscesses of the liver.

THE INCIDENCE OF COINCIDENT PROSTATIC CALCULI, PROSTATIC HYPERPLASIA AND CARCINOMA OF THE PROSTATE GLAND

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AND
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Previous to 1927 it was the opinion of most men interested in urology that prostatic calculi were rarely if ever associated with prostatic carcinoma. It was not until Kretschmer[1] reported 76 cases of prostatic calculi (in 5 of which prostatic carcinoma also was present) that it became generally appreciated that prostatic carcinoma and calculi could occur together.

The practical significance of estimating the incidence of prostatic calculi associated with prostatic hyperplasia and carcinoma of the prostate gland lies largely in the differential diagnosis of prostatic calculi and prostatic carcinoma. For years it has been emphasized that it may be impossible to distinguish a prostatic calculus from prostatic carcinoma by palpation. This problem of differential diagnosis was believed to have been solved by the use of roentgenographic studies of the prostatic region. This was particularly true in the minds of those who believed that prostatic calculi and carcinoma rarely if ever occurred together. Similarly, it often has been stated that prostatic calculi and prostatic hyperplasia are commonly associated, while calculi and carcinoma rarely occur together. This led to the implication that a prostatic calculus that is not associated with prostatitis probably denotes hyperplasia. In an effort to determine the validity of these deductions, this investigation was undertaken. Our purpose was to determine how frequently prostatic calculi are found associated with either prostatic hyperplasia or carcinoma.

This study is based on 4,136 cases of prostatic hyperplasia and 686 cases of carcinoma of the prostate gland in which transurethral resection was performed at the Mayo Clinic in a period of five years, that is from 1938 to 1942 inclusive. Roentgenographic examination of the prostatic region was made in all of these cases. These figures do not include cases in which transurethral resection was performed for the removal of calculi that were not associated with hyperplasia or carcinoma, or cases in which satisfactory roentgenographic visualization of the prostatic region was not obtained. Endogenous prostatic calculi were present in 288, or 7 per cent, of the 4,136 cases of hyperplasia (table 1) and in 43, or 6.3 per cent, of the 686 cases of carcinoma (table 2).

TABLE 1.—*Incidence of Prostatic Calculi in Cases of Hyperplasia of the Prostate Gland*

Year	Hyperplasia, Cases	Cases in Which Calculi Also Were Present	
		Number	Per Cent
1938	749	47	6.3
1939	783	43	5.5
1940	812	45	5.5
1941	775	66	8.5
1942	1,017	87	8.6
Total	4,136	288	7

TABLE 2.—*Incidence of Prostatic Calculi in Cases of Carcinoma of the Prostate Gland*

Year	Carcinoma, Cases	Cases in Which Calculi Also Were Present	
		Number	Per Cent
1938	116	7	6.0
1939	125	7	5.6
1940	129	8	6.2
1941	141	10	7.1
1942	175	11	6.3
Total	686	43	6.3

SUMMARY

A study of a large series of cases suggests that the incidence of prostatic calculi in cases of hyperplasia and in cases of carcinoma of the prostate is practically identical. This is in disagreement with the commonly accepted dictum that prostatic calculi are rarely found in cases of carcinoma of the prostate gland.

Number of Clinics.—There were 150 clinics in the country in 1900, 2,300 in 1910, nearly 4,000 in 1920, more than 6,000 in 1930. In 1931, 3,456 out of 6,571 clinics in the United States reported over thirty million visits; for all of the clinics in the country, including those not reporting, the number of visits in 1931 is estimated at forty million. A sharp increase in attendance in clinics maintained by the public authorities is reported in nearly every part of the country. A municipal hospital in the Middle West reports a growth in its daily outpatient service from 250 in 1931 to 800 in 1932. The outpatient department of a great municipal hospital in New England reports that daily visits averaged 900 in 1931 and nearly 1,500 in 1932. New York City experienced in 1931 an increase in dispensary attendance of nearly two million visits, equivalent to the entire growth of such attendance during the eight preceding years.—The Hospital in Modern Society, edited by Arthur C. Bachmeyer and Gerhard Hartman, New York, Commonwealth Fund, 1943.

10. Solowey, M.: A Serological Classification of Viridans Streptococci with Special Reference to Those Isolated from Subacute Bacterial Endocarditis, J. Exper. Med. **76**: 109-126 (July) 1942. Keith, H. M., and Heilman, I. R.: Subacute Endocarditis Due to Hemolytic Streptococci of Lancefield Group G, Am. J. Dis. Child. **65**: 77-80 (Jan.) 1943.

11. Rantz, L. A.: The Hemolytic Streptococci: Studies on the Carrier State in the San Francisco Area, J. Infect. Dis. **69**: 248-253 (Nov.-Dec.) 1941.

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13. Keefer, C. S. and others: Penicillin in the Treatment of Infections, J. A. M. A. **122**: 1217-1224 (Aug. 28) 1943.

From the Section on Urology, Mayo Clinic.

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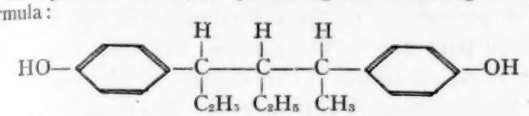
Council on Pharmacy and Chemistry

NEW AND NONOFFICIAL REMEDIES

THE FOLLOWING ADDITIONAL ARTICLES HAVE BEEN ACCEPTED AS CONFORMING TO THE RULES OF THE COUNCIL ON PHARMACY AND CHEMISTRY OF THE AMERICAN MEDICAL ASSOCIATION FOR ADMISSION TO NEW AND NONOFFICIAL REMEDIES. A COPY OF THE RULES ON WHICH THE COUNCIL BASES ITS ACTION WILL BE SENT ON APPLICATION.

AUSTIN E. SMITH, M.D., Secretary.

OCTOFOLLIN. — 2,4-di(*p*-hydroxyphenyl)-3-ethyl hexane. —$C_{20}H_{26}O_2$.—M. W. 298.41. Octofollin is one pair of racemates of the synthetic substance possessing the following structural formula:



Actions and Uses.—This compound when introduced into the human body orally and by injection provokes a response similar to that caused by other estrogenic substances. It is claimed to have a low incidence of toxicity. Contraindications are similar to those of other estrogens.

Dosage.—By biologic assay, 1 mg. of Octofollin is reported to be equivalent to approximately 25,000 international units or to 1,250 rat units of estrone. Average dose in tablets is about 2 or 3 mg. and in injection from 2 to 5 mg. This may be repeated daily for four to seven days until the dosage requirement is determined by clinical observation.

Tests and Standards.—

Octofollin is an odorless, white, crystalline powder which melts at from 164 to 166 C. It is readily soluble in acetone, ether, ethanol, methanol and dilute sodium hydroxide solution; soluble in vegetable oils; moderately soluble in glacial acetic acid; slightly soluble in benzene, chloroform, petroleum ether and dilute ethanol; practically insoluble in water and in dilute mineral acids.

Dissolve 10 mg. of octofollin in 2 cc. of concentrated sulfuric acid: a pale yellow color is produced which persists on dilution with water *(distinction from diethylstilbestrol, which yields an orange color)*. Add a few drops of 50 per cent solution of antimony pentachloride in dry alcohol-free chloroform to a very dilute solution of octofollin in the same solvent: a green colored solution which rapidly changes to brown is produced *(distinction from diethylstilbestrol, which yields a red or bluish red color)*.

Add 1 cc. of benzoyl chloride to 0.1 Gm. of octofollin contained in a test tube; heat and maintain gentle boiling for five minutes; cool, add 20 cc. of normal sodium hydroxide and shake the mixture thoroughly until a white solid mass separates. Filter, wash the precipitate with water and recrystallize twice from hot ethanol: the melting point of the 2,4-di(*p*-hydroxyphenyl)-3-ethyl hexane dibenzoate obtained is from 118 to 120 C.

Dissolve 0.1 Gm. of octofollin in 5 cc. of ether: the solution is clear and colorless. Dissolve 0.1 Gm. of octofollin in 5 cc. of previously neutralized 75 per cent ethanol solution: the solution is neutral.

Dry an accurately weighed specimen of octofollin at 100 C. for one hour: the loss in weight does not exceed 0.1 per cent. Ignite an accurately weighed specimen of octofollin after the addition of sulfuric acid: the residue is not more than 0.05 per cent.

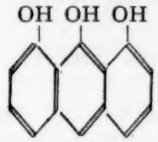
Transfer 0.1 Gm. of octofollin, accurately weighed, to a 100 cc. volumetric flask, add 6 cc. of 10 per cent sodium hydroxide solution and 30 cc. of distilled water; shake to dissolve the octofollin, then dilute to the mark with distilled water. Transfer exactly 20 cc. of the solution to a 250 cc. iodine flask fitted with an accurately ground stopper; add 10 cc. of freshly distilled carbon tetrachloride and 10 cc. of 10 per cent hydrochloric acid. Wet the stopper with distilled water; insert the stopper and shake the flask and contents to dissolve the precipitated octofollin in the carbon tetrachloride layer. Place 2 to 3 cc. of water around the stopper and cautiously remove it, avoiding loss of contents on release of compressed vapor. Rinse down the neck and walls of the flask with 3 to 5 cc. of distilled water. Add exactly 20 cc. of tenth-normal bromide-bromate solution down the wall of the flask and quickly insert the stopper, avoiding possible loss of bromine vapor. Shake the flask and contents thoroughly for several minutes. Place about 5 cc. of 10 per cent potassium iodide solution around the stopper and let the flask stand in the dark for thirty to forty minutes at 25 to 30 C. At the end of this period allow the sodium iodide solution to enter the flask, avoiding loss of vapor from within; place 3 to 5 cc. of distilled water around the stopper and allow it to rinse in the sodium iodide solution. Stopper the flask tightly and shake thoroughly. Let the mixture stand for five minutes and then titrate with tenth-normal sodium thiosulfate solution, shaking the mixture thoroughly after each addition of the reagent. The end point of the titration is reached when on addition of a fraction of a drop of the sodium thiosulfate solution followed by thorough shaking of the mixture the pink color of iodine in the carbon tetrachloride layer disappears. Each cubic centimeter of tenth-normal bromide-bromate solution is equivalent to 3.730 mg. of octofollin: the amount of octofollin found is not less than 99 per cent nor more than 101 per cent.

SCHIEFFELIN & COMPANY, NEW YORK

Solution Octofollin: 10 cc. multiple dose, rubber capped vials, 5 mg.

Tablets Octofollin: 0.5 mg., 1.0 mg., 2.0 mg. and 5.0 mg.

ANTHRALIN. — Signolin. — Dihydroxy-anthranol — 1,8,9-anthratriol.—$C_{14}H_{10}O_3$.—M. W. 226.22. Anthralin may be represented by the following structural formula:



Actions and Uses.—Anthralin is recommended as a substitute for chrysarobin in the treatment of psoriasis, having the advantage of less liability to production of dermatitis, less tendency to produce conjunctivitis when used about the face and scalp and less tendency to discoloration of the skin. The preparation has also been recommended in the treatment of chronic dermatomycosis and for stimulating action in chronic dermatoses.

Dosage.—Anthralin is generally employed in concentrations of from 0.1 per cent up to 1.0 per cent in ointments or creams. It is always well to begin with smaller dosages because of a tendency to produce an irritation of the skin.

Tests and Standards.—

Anthralin occurs as an odorless and tasteless, yellow, crystalline powder, which is readily soluble in chloroform, soluble in acetone, benzene and pyridine, slightly soluble in alcohol, ether and glacial acetic acid and insoluble in water. It is soluble in sodium hydroxide solution, yielding a yellow to orange colored solution possessing greenish fluorescence. Alkaline solutions of anthralin rapidly oxidize in air, lose fluorescence and become a deep orange-red. The melting point of anthralin is from 175 to 181 C.

Dissolve about 0.1 Gm. of anthralin in 10 cc. of alcohol, and 0.1 cc. of diluted ferric chloride solution: a greenish brown color results. Add a few crystals of anthralin to 2 cc. of sulfuric acid: an orange-yellow color results *(1,8-dihydroxy-anthraquinone gives a scarlet color)*.

Dissolve 0.1 Gm. of anthralin in 10 cc. of warm acetone: the solution is clear; pour the solution into 200 cc. of water: a yellow precipitate results; add 5 cc. of sodium hydroxide solution and mix: the precipitate dissolves and the yellow colored solution rapidly changes to orange and finally to red.

Add about 0.5 Gm. of anthralin to a mixture of 3 cc. of anhydrous pyridine and 3 cc. of acetic anhydride and boil about fifteen minutes. Pour the mixture on crushed ice, collect the precipitate and recrystallize twice from glacial acetic acid: the melting point of the yellow needle shaped crystals of triacetyl anthralin obtained is from 208 to 210 C., with sublimation.

Add 0.5 Gm. of anthralin to 10 cc. of water, mix and filter: the filtrate is neutral; separate portions of the filtrate yield no turbidity on the addition of silver nitrate solution, barium nitrate solution or ammonium sulfide solution, and no color on the addition of ferric chloride solution.

Ignite 0.5 Gm. of anthralin: the ash is negligible.

Transfer 0.1 Gm. of anthralin, accurately weighed, to a beaker, add 75 cc. of acetone and warm to dissolve the solid. While the solution is hot, add 10 cc. of silver ammonium nitrate solution (dissolve 3 Gm. of silver nitrate in 120 cc. of water and add 10 cc. of 10 per cent ammonium hydroxide solution), mix and allow to stand at room temperature for two hours. Filter through a suitable Gooch crucible (or sintered glass filter). Wash the beaker and precipitate with ether, acetone, then about 300 cc. of ammoniacal ammonium nitrate solution (dissolve 15 Gm. of ammonium nitrate in 300 cc. of water and add 10 cc. of ammonium hydroxide solution) and finally wash with acetone. Place the filter in the beaker used for the precipitation of silver, add 10 cc. of water and 10 cc. of nitric acid and heat to near boiling to facilitate solution of the silver. Add enough water to cover the filter and boil gently for twenty minutes. Add 0.5 Gm. of chloride free decolorizing charcoal, mix, let stand for ten minutes and filter while hot through paper. Rinse the beaker and crucible with hot water and finally wash the paper and residue with hot water; combine the filtrate and washings. Cool and titrate with tenth-normal ammonium thiocyanate, using 5 cc. of ferric ammonium sulfate solution, acidified with nitric acid, as the indicator. Each cubic centimeter of tenth-normal ammonium thiocyanate is equivalent to 0.01079 Gm. of silver. The amount of silver precipitated, calculated from the titration, is not less than 1.35 times and not more than 1.45 times the amount of anthralin taken.

ABBOTT LABORATORIES, NORTH CHICAGO, ILL.

Anthralin Ointment: 0.1%, 0.25%, 0.5% and 1%. Anthralin in petrolatum base.

Anthralin Cream: 0.1%, 0.25% and 0.5%. Anthralin in a vanishing cream base of potassium stearate, glycerin and distilled water.

BACTERIAL VACCINE MADE FROM BRUCELLA (Undulant Fever Vaccine) (See New and Nonofficial Remedies, 1943, p. 552).

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SATURDAY, MARCH 4, 1944

THE SULFONAMIDES

The favorable effects of the widespread clinical use of the sulfonamide compounds [1] is now reflected in statistics of mortality. Investigations of the principles which govern their effectiveness, as well as interest in chemotherapy in general, have been stimulated. A symposium by the New York Academy of Sciences [2] presents much recent information.

The action of the sulfonamides is best evident in disease produced by certain organisms and characterized by acute onset with rapid invasion of the tissues. Rapid invasion is in part concerned with rapid growth of bacteria; the curative action of the sulfonamides is no doubt one of bacteriostasis.

The manner in which sulfonamides produce bacteriostasis is partially understood. The inhibition of the action of sulfonamides by para-aminobenzoic acid is well known. In addition amino acids such as methionine, aminoacetic acid, serine and xanthine have been shown to alter, under certain conditions, the sulfonamide effect. At present it is thought that para-aminobenzoic acid is an essential metabolite for bacterial growth and that there is competitive inhibition by the sulfonamides of the enzyme systems in which it is normally involved.

In order to affect bacteriostasis the sulfonamide compound must reach the bacteria in effective concentration. This means, among other things, that there must be adequate blood supply to the lesion. However, the important factors which influence the attainment of an effective concentration are the absorption, distribution and ultimate excretion of the drugs.

The rate and degree of absorption of the various compounds differ. Use is made of the fact that the gastrointestinal absorption of compounds such as succinylsulfathiazole is low, while that of other compounds, such as sulfamerazine, is rapid and complete.

The commonly used sulfonamides are diffusible throughout all of the body water and appear in the various fluid compartments. In addition, sulfapyridine, sulfathiazole and sulfamethylthiazole are actually concentrated within certain tissue cells. In the cerebrospinal fluid the concentration, relative to the blood concentration, is somewhat lower for all sulfonamide compounds. This is in part due to the tendency of the sulfonamides to combine with plasma proteins, forming a nondialyzable fraction, and in part to the mechanism of formation of the cerebrospinal fluid. The extent of the plasma binding is sulfadiazine 20 per cent, sulfapyridine 30 per cent, sulfamerazine 40 per cent and sulfathiazole 60 per cent.

The persistence of the sulfonamides in the tissues is in large part due to the manner and thus the rate of their renal excretion. The degree of plasma binding may be concerned in this process. However, the blood concentration and the type of renal tubular phenomena are the most important factors. Sulfathiazole and sulfamethylthiazole are excreted from the body relatively rapidly because they are reabsorbed little, if any, in the tubules. However, sulfapyridine, sulfadiazine and sulfamerazine are slowly eliminated because of substantial and perhaps active tubular reabsorption.

In the metabolism of the sulfonamide compounds the body converts them in part into less bacteriostatic, acetylated forms. These acetylated forms are also eliminated in the urine and there is some indication that in the case of sulfathiazole the high incidence of renal complications may be due to the rather poor solubility of the acetylated form at the p_H of the urine.

The question of the toxicity of the sulfonamides is important but not well understood. The toxic phenomena are related to the blood concentration of these agents and the duration of treatment with them. The absence of any striking increase in the incidence of toxic phenomena with intentionally excessive blood concentrations or excessively prolonged therapy indicates that these are not the sole factors. To say that toxic reactions not explainable by excessive blood levels or a too prolonged administration are due to idiosyncrasy is begging the question, since so little is known relative to aberrant drug responses. Sensitization appears to assume a role in some cases. The recent observations that in animals the administration of some of the less absorbable sulfonamides causes vitamin deficiencies by decreasing the numbers of Escherichia coli which synthesize these vitamins in the gastrointestinal tract [3] suggest another mechanism by which toxic phenomena may be brought about.

The relatively simple chemical structure of the sulfonamides has led to a certain degree of correlation between physical and chemical properties and bacteriostatic action, so that the chemist can in part predict the potency of new compounds. However, owing to the absence of such information relative to toxicity, the usefulness of newer sulfonamides awaits actual animal and clinical study.

1. Stocks, Percy: Vital Statistics of 1942, Lancet **1**: 672, 1943.
2. Annals of the New York Academy of Sciences **44**: 445, 1943.
3. Elvehjem, C. A.: Present Status of the Vitamin B Complex, American Scientist **32**: 25, 1944.

GENETIC FACTORS IN TUBERCULOSIS

Although exposure to infection is an important factor in the etiology of tuberculosis, variability in individual susceptibility or resistance may be a function of the genetic constitution. Lurie's work [1] in inbred rabbit stocks is one of the most extensive documented experimental approaches to this thesis. Consistent inbreeding of rabbits led to the development of three different family groups with respect to the resistance to natural or experimental tuberculosis: a highly resistant family displaying a localized chronic ulcerative form of pulmonary tuberculosis on inoculation with large doses of bacilli, several nonresistant families in which a rapidly progressive and generalized disease occurred and some moderately resistant families showing various intermediate forms of the disease. Lurie concluded that the resistance of rabbits to naturally or artificially acquired tuberculosis is largely controlled by their genetic constitution.

By using the so-called twin method in a statistically representative number of cases, Kallmann and Reisner [2] have found Lurie's conclusions valid in spontaneous human tuberculosis. The significance of the twin method depends on the distinct hereditary differences between the categories of monozygotic and dizygotic twins. Monozygotic twins occur as the result of the division of the embryo at an early stage of development. Since the two halves are derived from a single fertilized ovum, each will carry precisely the same complement of genes. Such twins are always of the same sex and are genetically as identical as the right and left halves of a single individual. Dizygotic twins result from two separate ova which were fertilized at the same time. Genetically they are no more alike than any other pair of brothers and sisters who are born at different times.

The twin index cases were collected from tuberculosis hospitals and clinics in New York. The study included 308 pairs consisting of 616 twins, of whom 334 were index cases affected by reinfection tuberculosis. There were 78 monozygotic and 230 dizygotic twin pairs. In addition to 616 twin partners the investigation was extended to 930 full siblings, 74 half siblings and 226 marriage partners of the twin partners. Comparison of the morbidity rates in these families disclosed that the chance of developing tuberculosis increased in strict proportion to the degree of blood relationship to the tuberculous index case. In 87.3 per cent of the monozygotic twins, both partners had reinfection tuberculosis. In contrast, only 25.6 per cent of the dizygotic partners of the index case developed the disease. The morbidity rate among the other members of the families amounted to 25.5 per cent in the full siblings, 11.9 per cent in the half siblings and 7.1 per cent in the marriage partners. This direct correlation between consanguinity and incidence of tuberculosis was remarkably consistent and undoubtedly specific. When, in addition, the lack of correlation between opportunities for exposure and frequency of tuberculosis is considered, it seems most likely that the differences in morbidity rate were essentially dependent on genetic differences. Moreover, the morbidity rate in the monozygotic cases was independent of the occurrence or absence of tuberculosis in the parents, being largely determined by the identical genetic constitution as the tuberculous index cases. Likewise a genetic mechanism was found to modify individual resistance to tuberculosis, as evidenced by the demonstration of similarities in extent, course and outcome of the disease in the monozygotic twin partners. Similar behavior to the disease was about eight times more frequent than dissimilar behavior in monozygotic twins, while it was only half as frequent in dizygotic twin partners. Statistically the possibility of dying from tuberculosis is practically zero for a tuberculous monozygotic twin if the other partner remains free from tuberculosis despite definite exposure to infection. Resistance to the disease was definitely a function of the genetic constitution.

1. Lurie, M. B.: Heredity, Constitution and Tuberculosis: An Experimental Study, supplement to Am. Rev. Tuberc. **44:** 1 (Sept.) 1941.
2. Kallmann, F. J., and Reisner, David: Twin Studies on Genetic Variations in Resistance to Tuberculosis, J. Heredity **34:** 269 (Sept.), 293 (Oct.) 1943.

THE MICROBIOLOGIC MEASUREMENT OF AMINO ACIDS

A normal life process is impossible unless each of the essential amino acids is furnished the organism. Moreover, the biologic value of each of the proteins in food is also dependent on the relative composition of these essential amino acids. Obviously, therefore, the measurement of these building stones of protein should be accurate and readily available.

Until now the quantitative measurement of the amino acids in food and other proteins has been relatively easy only in some cases. Many of these amino acids are closely related chemically. Many exist in optically active forms which must be differentiated; in certain instances only the levorotatory form can be utilized by the organism, while the dextrorotatory is without value in the synthesis of protein. This is important, because many synthetic amino acids have become available as racemic mixtures.

Study of bacterial growth has furnished an interesting and important solution of this quantitative problem. It has been referred to as a microbiologic method and introduces a new approach to the quantitative measurement of certain biologic substances essential for bacterial growth and present in food and in tissues. The first demonstration of the value of this method was reported only a few years ago by Snell and Wright [1] in the chemistry department of the University of Texas.

1. Snell, E. E., and Wright, L. D.: Biol. Chem. **139:** 675 (June) 1941.

They found that nicotinic acid (niacin) could be measured accurately by following the growth of Lactobacillus arabinosus on a purified basal medium lacking only this vitamin and to which various amounts of the unknown is added. They found that this method was rapid and accurate and compared well with the chemical and the dog method which had been previously employed. Moreover, they were able to determine with an accuracy of 8 per cent of nicotinic acid added to various tissues which were thus analyzed. The establishment of the quantitative requirements of amino acids by growing bacteria [2] naturally led to the employment of this method for the determination of various amino acids. Shankman, Dunn and Rubin [3] at the University of California at Los Angeles presented a series of analytical data and found that this method yielded an average accuracy of 3.3 per cent as determined by the results obtained by adding known amounts of amino acids to the basal medium. Later these workers [4] used another bacterium, Lactobacillus casei, and reported determinations for glutamic acid, leucine, phenylalanine, tryptophan, tyrosine and valine. In a paper appearing at the same time from the Texas Agricultural Experimental Station, Kuiken and his co-workers [5] determined accurately values for valine, leucine and isoleucine with Lactobacillus arabinosus.

This new method is apparently precise, because growing bacteria have rigid requirements for the various amino acids and are able to discriminate not only between the natural and unnatural forms but also the various amino acids closely related as, for example, leucine and isoleucine. Should this new method become widely used and its accuracy confirmed by other workers, it will undoubtedly open a new era in our knowledge of the amino acid composition not only of food proteins but also of the various tissue proteins and body fluids. In the past the biologic value of proteins was determined almost entirely by growth experiments, by nitrogen balance experiments or by the ability of the organism to synthesize plasma proteins and in only a limited way by their chemical composition. While analysis of certain amino acids such as tryptophan and tyrosine is satisfactory, this new method is undoubtedly a great advance in the determination of many of the others. Moreover, it requires much smaller samples than many of the older methods. Thus it will be possible to restudy more precisely and more accurately the full amino acid composition of many of the food proteins. Moreover, it will perhaps stimulate many advances in our knowledge of the behavior of amino acids within the fluids and tissues of the animal organism where they are present in small concentrations, as for example in the circulating plasma. The picture of protein and amino acid metabolism is now known to be rapidly changing and therefore requires more accurate analytical procedures even to fill in its broad outlines, not to mention its finer details.

2. Shankman, S.: J. Biol. Chem. **150:** 305 (Oct.) 1943.
3. Shankman, S.; Dunn, M. S., and Rubin, L. B.: J. Biol. Chem. **150:** 477 (Oct.) 1943.
4. Shankman, S.; Dunn, M. S., and Rubin, L. B.: J. Biol. Chem. **151:** 511 (Dec.) 1943.
5. Kuiken, K. A.; Norman, W. H.; Lyman, C. M.; Hale, Fred, and Blotter, Lois: J. Biol. Chem. **151:** 615 (Dec.) 1943.

Current Comment

CLINICAL RECOGNITION OF CORONARY THROMBOSIS

On the insistence of his professional friends, Dr. James B. Herrick somewhat reluctantly consented to tell of his early experiences with coronary occlusion.[1] As early as 1910 he was called to see a man who was seized one hour after a moderately heavy midnight meal with severe pain in the lower precordial region. The patient's mind was clear. There was moderate cyanosis and some dyspnea. The chest was full of fine and coarse moist rales. There was a running feeble pulse of 140. The patient died fourteen hours after the onset of pain. Impressed with reading of the case of Panum, which resembled this case closely, Dr. Herrick told Dr. Hektoen, who was to perform the necropsy, that he would most likely find a "clot in the coronary artery." The postmortem examination revealed a red thrombus completely occluding the coronary artery a short distance from its origin, well defined areas of yellowish and reddish softening in the wall of the left ventricle and acute fibrinous pericardial deposit over the left ventricle. Shortly afterward Dr. Herrick was able to make an antemortem diagnosis of coronary occlusion in a man who lived seven days after the onset of pain. From his observations on these 2 cases and from an exhaustive study of medical writings, Dr. Herrick derived a theoretical conclusion that "there is no inherent reason why the stoppage of a large branch of a coronary artery, or even of a main trunk, must of necessity cause sudden death. Rather may it be concluded that, while sudden death often does occur, at times it is postponed for several hours or even days, and in some instances a complete, i. e. functionally complete, recovery ensues." Coronary thrombosis was, of course, well known to early pathologists and was accurately described by many, to quote only René Marie and M. Sternberg. Its true clinical significance was, however, little appreciated either in Europe or in the United States. The next step in the evaluation of our knowledge of coronary occlusion was the demonstration by Dr. Fred Smith, Dr. Herrick's associate, "that a fairly constant change in the electrocardiogram was brought about by ligation of coronary arteries in the dog, so that one could predict with reasonable certainty the alteration that would appear in the tracing after experimental stopping of circulation in particular branches." These observations were reported by Dr. Smith in the *Archives of Internal Medicine* in July 1918.

1. Herrick, J. B.: An Intimate Account of My Early Experience with Coronary Thrombosis, Am. Heart J. **27:** 1 (Jan.) 1944.

This important clinical contribution is a demonstration of the power of scientific observation and of analysis. Dr. Herrick firmly believed that discoveries in the clinical field did not depend exclusively on the use of elaborate instruments and laboratory methods. He expressed this idea clearly in one of his early papers on the subject: "This address, if it accomplishes its aim, will encourage the specialist and the research worker to go forward with the use of the newer instruments and with the investigations by which new facts concerning the heart will come to light. It will also, I trust, encourage the general practitioner to retain some of his old self confidence and not to lose faith in his powers of observation and in his ability to analyze subjective symptoms; and still to believe that it is possible by well established methods of physical diagnosis to understand many of the anatomic, pathologic and physiologic conditions of this important organ."

TREATMENT OF HAEMOPHILUS INFLUENZAE INFECTIONS

In view of the conflicting opinions as to the most effective agent for the treatment of influenzal meningitis in children, Alexander and Leidy [1] analyzed the comparative value of sulfonamide drugs and serum in experimental influenzal infections. Type B Haemophilus influenzae obtained from spinal fluid was suspended in mucin, which enhances its virulence and permits experimental studies with small numbers of organisms. The mouse protection test, which has been thoroughly standardized, and the inhibitory capacity on culture growth of the organism were used in the determination of the effectiveness of serum and sulfonamide drugs. There was a direct correlation between the protective value of these agents in mouse infections and their inhibitory capacity in test tubes. Of the sulfonamides tested, sulfadiazine proved to be the most effective drug. In mice 0.4 mg., yielding a blood concentration of 1.6 mg. per hundred cubic centimeters after twenty hours, was effective in protecting against 1,000 minimal lethal doses. Sulfapyridine was much less effective, as a dose fifteen times higher than that of sulfadiazine was required to provide identical protection. Sulfanilamide was the poorest drug in this respect. Only huge lethal doses had some degree of effectiveness against 1,000 minimal lethal doses. As compared to sulfadiazine, type specific rabbit antibody proved to possess equal protective value against H. influenzae mouse infections. However, regardless of the dose administered and of the blood concentration obtained, both sulfadiazine and serum, when used singly, failed to protect regularly when the dose of organisms inoculated exceeded 10,000 minimal lethal doses and were completely ineffective against 1 million minimal lethal doses. When serum and sulfadiazine were combined, the mice regularly withstood 1 million minimal lethal doses. The synergistic action of these two agents is of great importance in the treatment of severe B type H. influenzae meningitis in infants and children, in which the death rate may be reduced to a minimum by the combined use of serum and sulfadiazine.

1. Alexander, Hattie E., and Leidy, Grace: Experimental Investigations as a Basis for Treatment of Type B Haemophilus Influenzae Meningitis in Infants and Children, J. Pediat. **23**: 640 (Dec.) 1943.

ROENTGEN THERAPY OF GAS GANGRENE

On February 9 the Associated Press carried a story from Omaha to the effect that Dr. James F. Kelly, Omaha physician and x-ray physician at Creighton University, had charged that sulfonamides are being used ineffectively in the treatment of the war wounded suffering from gas gangrene in cases in which x-ray therapy would halt or prevent infection and make amputation of legs and arms unnecessary. According to the item from the Associated Press, Dr. Kelly had asserted that "the United States Public Health Service and the National Research Council had failed to investigate thoroughly the use of x-ray in prevention of wound infection and the American Medical Association had failed to report favorable results attained from x-ray." Following publication of this item, the Office of the Surgeon General of the United States Army requested the National Research Council, through the Subcommittee on Radiology of the Division of Medical Sciences, to consider the matter. This was done immediately and the following resolution was adopted:

> The place of x-ray therapy in the management of cases of gas gangrene has been a concern of this Committee for several years. In future as in the past, the Committee will continue to concern itself with this problem. The present opinion of the Committee based upon continuing study of the work of many investigators is that, up to the present time, the effectiveness of x-ray in the treatment of gas gangrene has not been established. For this reason, the use of x-ray therapy in gas gangrene is still experimental.

The Subcommittee on Radiology also approved the statement from the Office of the Surgeon General of the United States Army with regard to the treatment of war wounds with x-rays prepared by the Technical Information Branch on February 9. Both of these actions of the Subcommittee on Radiology have been approved by the chairman of the Committee on Surgery and also by the Subcommittee on Infected Wounds and Burns of the National Research Council.

ARMY SPECIALIZED TRAINING PROGRAM FOR PREMEDICAL AND MEDICAL STUDENTS TO BE CONTINUED

Information received as THE JOURNAL goes to press indicates that the needs of the armed forces and the civilian population for a continuing supply of physicians have been recognized. Announcement is made that both premedical and medical students will be continued under the Army Specialized Training Program as heretofore. Just how long the program will be continued with government support has not yet been stated. However, the actions taken by the Selective Service System with the approval of the Army and Navy indicate that there is every intention to defer medical and premedical students in recognized institutions who maintain proper standards of scholarship, whether or not the A. S. T. P. is continued.

MEDICINE AND THE WAR

In this section of The Journal each week will appear official notices by the Committee on War Participation of the American Medical Association, announcements by the Surgeons General of the Army, Navy and Public Health Service, and other governmental agencies dealing with medicine and the war, and such other information and announcements as will be useful to the medical profession.

AMERICAN CIVILIANS IN A JAPANESE INTERNMENT CAMP

Frank E. Whitacre, M.D.
Recent Repatriate on M/S Gripsholm
SYLVANIA, OHIO

During the first few weeks of internment in a Japanese concentration camp at Manila, Philippines, a group of 3,900 internees (about 80 per cent Americans), with courageous spirit and without help from the Japanese, organized themselves into a smooth running community, of which the hospital formed an important part. A few hours after Pearl Harbor the Japanese were attacking the Philippines in force. A few civilian physicians assisted in the Sternberg military base hospital until the hospital was closed at the time of the retreat to Bataan. Most of our seriously wounded men from the bombings at Clark, Nichols and Nielson airfields, and also from the Cavite naval yard, were transferred the latter part of December to Australia on a hospital ship. The fall of Manila was imminent, and we remained at our hotel until the Japanese army entered the city on Jan. 2, 1942.

THE CAMP AT SANTO TOMAS

On January 5 we were taken in trucks and busses to Santo Tomas internment camp. Santo Tomas is the oldest university under American protection and consists of some 50 acres and thirteen buildings. About two thirds of the acreage and most of the buildings were turned over to us by the Dominican Fathers. This gave each person only about 30 square feet of floor space. The Japanese did not furnish beds, bedding or cots but allowed us to obtain a few necessities wherever we could. The American aptitude for organization was soon in evidence. The Japanese did not look after details of organization and management but permitted the internees to do that themselves. An executive committee was elected, with a chairman responsible to the Japanese commandant. Various committees were formed, including finance and supply, sanitation and hygiene, order and safety, construction, work assignment, kitchens, medical attention, education, religion, recreation and entertainment, and in fact committees to cover all of the main functions required in the operation of a community of this size.

SUPPLIES FROM THE RED CROSS

For the first few months our food and supplies came from Red Cross organizations. On July 1, 1942 the Japanese government for the first time began to supply funds for the support of the camp: 70 centavos (35 cents) a day per person. Later this was increased to 1 peso (50 cents), which had to take care of everything for the support of the camp; electricity, water and all supplies, including food. There were three kitchens, which were operated by the internees in a clean and efficient way. Two meals were served "on the line" daily, consisting of rice, green vegetables, a small amount of meat twice a week and occasionally fruit. Although fruit is abundant in the Philippines, the lack of transportation reduces the available supply. Persons with sufficient funds were permitted to have food sent in to them, usually one cooked meal a day, and this "package line" served about 1,000 persons. In twenty-two months we each received two Red Cross gift packages, from Johannesburg, South Africa, and Toronto, Canada, respectively. The average diet provided only approximately 1,800 calories a day, containing about 50 Gm. of protein and around 30 Gm. of fat; no more than half of the latter was obtained from animal sources. It is not surprising, therefore, that a loss of weight of from 30 to 50 pounds was common, and that borderline avitaminosis was prevalent.

ATTITUDE OF THE JAPANESE

The treatment of the internees by the Japanese was characterized chiefly by indifference. The close confinement and the lack of adequate food were a constant menace. During the first several months of internment about 1,000 sick and elderly persons were allowed to leave the camp if they could show that they had a place to stay and could be self supporting. But in May 1943, coincident with Premier Tojo's visit to Manila to offer the Philippines independence, almost all of these persons were brought back into camp. It was a pitiful sight, as room after room in the buildings used for sleeping quarters literally had to be converted into an old persons' home. The camp was already overcrowded, owing to the gradual accumulation of small groups brought in from time to time from the provinces. This reinternment necessitated the moving of 800 young and middle aged, able bodied men to Los Baños, 40 miles distant.

THE CAMP HOSPITAL

Medical attention was efficient, as far as this was possible. After one or two rooms had been used for the first few days, a small hospital of 80 beds was set up in a one story frame building which had been the metallurgy department of the university. This hospital was well defined into two women's wards and two men's wards, an outpatient department consisting of a waiting room, treatment room and facilities for minor surgery, and an adequate dental department. Perhaps it would be better not to mention any names at all in this brief report, but it seems only fair to mention two: Dr. Charles N. Leach of Burlington, Vt., a field director of the Rockefeller Foundation, was responsible for the organization and direction both of the hospital at Santo Tomas and of the hospital at Los Baños. Dr. Hugh L. Robinson of Auburndale, Mass., carried the load of individual medical attention. In August 1942 the hospital was moved to another building, which permitted better facilities and 120 beds. At present the physicians remaining with our people in the Philippines are doing the best they can with the supplies they have at hand.

The camp hospital was excellently staffed with nurses, at first from the internees, a few nurses from the Philippine Red Cross, and the Mary Knoll Sisters. A few months later eleven Navy and sixty Army nurses accepted this responsibility and continue to provide the best of nursing care.

HELP FROM THE FILIPINOS

We appreciated the brave and dependable Filipino people. Aside from invaluable assistance, both individually and collectively, to the internees, the officials of the Philippine General Hospital made available one 50 bed ward for men, which was always filled to capacity, and one 12 bed ward for women. In many instances the vaguest promise to pay sometime was sufficient during this emergency. Also complete medical, surgical, laboratory and roentgen ray facilities were provided whenever necessary.

EPIDEMICS

Among the medical conditions seen in the camp, the first to reach epidemic proportions was enteritis in the early spring of 1942. The causative organism was one of the salmonella group. This was shortly followed by amebic dysentery. In July an arrogant and officious major of the Japanese military medical service investigated the camp and was very unkind to the director of our hospital, who was in no way to blame for the wave of enteric conditions affecting the camp. Many typical cases of dengue fever, as well as influenza, were seen in the early months of internment. This was followed by an epidemic of about 150 cases of catarrhal jaundice. Also malaria was present among people brought in from the provinces, but there was no malaria which could be traced to the Manila area. About 12 patients with anterior poliomyelitis were seen, and shortly thereafter approximately the same number were afflicted with herpes zoster. Venereal diseases were prevalent only during the first few months, at which time 50 patients with syphilis were treated. Some 20 patients with active pulmonary tuberculosis were segregated from the sleeping rooms. A survey of the camp, involving two thousand fluoroscopic examinations, added to the protection of all persons. About 150 persons were grouped and catalogued as blood donors in order to be prepared should occasion for their need arise, and they have been very useful.

No epidemics have occurred among the 300-odd children, who are doing very well; milk supplies are reserved for them. The children have their separate hospital of 15 beds. The ordinary diseases of childhood have not been a serious problem, and fortunately scarlet fever is rare, if not unknown, in the Philippines.

The vitamin deficiencies previously mentioned are chiefly due to a lack of vitamin B_1, characterized by paresthesias and difficulty in focusing the eyes. Riboflavin deficiency was manifest by pigmentation around the nose and mouth, sore tongue and diarrhea. A few cases of pernicious anemia and sprue were seen; also many cases of diabetes and peptic ulcer. A considerable number of hernias, mostly inguinal, were probably due to the fact that middle aged and older men who had done office work all their lives found it necessary to do heavy work on an inadequate diet. It seemed that arteriosclerosis and enlargement of the prostate gland were at least as numerous as would be expected in a corresponding group living under normal conditions.

One should not fail to mention the mental retardation that accompanies confinement. Immediately following the bombings and in the early days of internment, occasional hysteria was seen, but after many months lethargy and mental deterioration affected a moderate number of persons.

MORTALITY

The number of deaths after twenty-two months is probably not much in excess of that found in a group of the same size in normal times. But it must be expected that the mortality rate will increase, for nutritional disturbances are growing and the drug and medical supplies situation is deplorable. There are no drugs for treating dysentery; the supply of insulin and liver extract is almost exhausted; there are practically no sulfonamide drugs, narcotics, anesthesias or glucose. It is to be hoped that out of the vast supplies sent to the Far East a fair portion of the vitally needed drugs and nutritious foods will be made available to our people in the Philippines to improve their gloomy situation. Better still, it is to be hoped that the many efforts of our government for further repatriations will be successful.

ARMY

PHYSICAL EFFICIENCY RATINGS FOR TRAINEES

Army Service Forces Circular No. 25 states that training in medicine under the Army Specialized Training Program will terminate on the issuance of a certificate of successful completion of the prescribed course of medical instruction. Graduates who are discharged from their enlisted status in order to accept appointment in the Medical Corps Reserve or Medical Corps, A. U. S., will not be called to active military duty until they have completed the nine months internship, as now prescribed, if the military situation permits. Such internships will be served in an inactive status, that is, as civilians, and will be contracted for individually by the prospective graduates during their senior years.

The War Department desires that the internship be served in hospitals approved for intern training by the Council on Medical Education and Hospitals of the American Medical Association, and that, in view of the need for interns in hospitals within the United States, contracts be not accepted for internships in Canadian hospitals. There is no objection to accepting and serving the prescribed hospital internship in the territories of the United States or the Canal Zone, in hospitals which will coordinate their intern-resident training programs with the accelerated medical program and with the intern-resident program of Procurement and Assignment Service for Physicians, Dentists and Veterinarians, War Manpower Commission.

In general, unless the exigencies of the military situation require earlier call to active duty, appointed medical officers will be ordered to active duty by the War Department not later than ten months after appointment, except that not to exceed one third of the total number of such interns available for call to active duty in any calendar month, if certified to the War Department by the War Manpower Commission (Procurement and Assignment Service for Physicians, Dentists and Veterinarians) as essential junior hospital residents within a ceiling quota for such residents allocated by that agency to each state and hospital, will be continued in an inactive status by the War Department for an additional period of nine months. One half of the number deferred from call to active duty as junior residents who are subsequently available for call to active duty in any calendar month will, if similarly certified, be continued on an inactive status for an additional period of nine months as senior residents.

Present plans contemplate that, on being ordered to active duty within ten months after appointment, or on completion of junior or senior residency, if authorized, officers will be sent to the Medical Field Service School for a period of approximately six weeks. It is further contemplated that those ordered to active duty within ten months after appointment will be assigned for a period of six weeks to an army general hospital prior to definite duty assignment.

COL. DALE G. FRIEND AWARDED LEGION OF MERIT FOR SOUTH PACIFIC ACTION

Col. Dale G. Friend, formerly of North Attleboro, Mass., was awarded the Legion of Merit for "exceptionally meritorious conduct in the performance of outstanding services as commanding officer of a medical regiment and as division surgeon of an infantry division from Jan. 19, 1942 to March 22, 1942 in the South Pacific Area." The citation accompanying the award read as follows: "Award of the Legion of Merit. Dale G. Friend, Colonel, Medical Corps, United States Army, for exceptionally meritorious conduct in the performance of outstanding services as commanding officer of a medical regiment and as division surgeon of an infantry division from Jan. 19, 1942 to March 22, 1942 in the South Pacific Area. Under Colonel Friend's leadership the medical regiment was brought to the highest standard of efficiency and provided excellent service in the field for the division during its successful combat operations at Guadalcanal. Due to his professional ability, zeal and ingenuity, the treatment of the sick and wounded and evacuation to higher medical echelons under extremely adverse conditions were marked by speed and efficiency of the highest order."

Dr. Friend graduated from Harvard Medical School, Boston, in 1935 and entered active service Jan. 16, 1941. He has served seventeen months overseas, six months of which was in combat.

INTERNS AND RESIDENTS HOLDING MEDICAL ADMINISTRATIVE CORPS COMMISSIONS URGED TO ACCEPT MEDICAL CORPS COMMISSIONS

There are still a few interns and residents who hold commissions in the Medical Administrative Corps who have failed to convert their commissions to the Medical Corps. Detailed instructions have been mailed to the remaining interns and residents, giving the procedure to be followed. In certain instances the conversion requests have been ignored, under the impression that a Medical Administrative Corps commission would assure a delay in a call to active duty. It has been pointed out that a failure to comply with the conversion requests within a reasonable period may result in an immediate call to duty as a Medical Administrative Corps officer. Every effort should be made by all concerned to comply with the requests of the Surgeon General and effect immediate conversion.

SOLDIER'S MEDAL AWARDED TO ARMY NURSE

The War Department recently announced the award of the Soldier's Medal to 1st Lieut. Orah D. Stephenson, Army Nurse Corps, chief nurse at the Station Hospital, Morris Field, Charlotte, N. C., for heroism in the rescue of a nurse from a burning building. Lieutenant Stephenson was awakened Nov. 9, 1943 by the smell of smoke from a fire in the nurses' quarters. She acted immediately to arouse other occupants of the building. Hearing a scream from one of the rooms, she fought her way through flames and smoke and found an unconscious nurse. Although the latter was much heavier than she, Lieutenant Stephenson dragged her to safety through the blazing hall. Lieutenant Stephenson was burned about the face and hands and was partly overcome by smoke. She was graduated in June 1929 as a nurse at the Jennie Edmundson Memorial Hospital, Council Bluffs, Iowa, and entered the Army Nurse Corps on Dec. 15, 1940 at Letterman General Hospital, San Francisco. She was promoted to chief nurse on Dec. 3, 1941. Lieutenant Stephenson is the third army nurse to receive the Soldier's Medal.

SEVENTH MEDICAL BATTALION CITED

The War Department recently announced the citation of the Seventh Medical Battalion. This unit accomplished rapid evacuation throughout the entire action on Attu Island despite extremely difficult terrain and unfavorable weather conditions. At all times collecting and clearing installations were kept in close support of the advancing troops. Even though the battalion was augmented during critical periods with a miscellany of other troops untrained in medical department duties and not organized to operate in small independent litter groups, it functioned capably under fire. On May 29, 1943 four medical installations of this battalion were overrun by the enemy. In all instances officers and enlisted men stayed with the wounded, giving them valuable medical aid. Although all four installations suffered casualties during the thirty-six hour period following this assault, by gallant efforts the majority of the wounded troops were evacuated alive when the enemy was cleared from the area.

ORIENTATION COURSE FOR OCCUPATIONAL THERAPISTS

Orientation courses for newly appointed occupational therapists will be conducted to make them familiar with the organization of the Army, of the medical department, of army hospitals, and with the particular problem of the care and treatment of sick and wounded military personnel, according to Headquarters Army Service Forces. Commanding generals of service commands will assign newly appointed occupational therapists within certain allocations to attend these courses and on completion of the course to report to the general hospital of permanent assignment. The initial appointment of such civilian occupational therapists should be so dated that on reporting for duty they can be sent immediately to the course. Travel from the place where the occupational therapist reports for duty to the general hospital where the course is given, and return to the hospital of assignment, will be at government expense. Orders governing such travel and per diem allowances will be issued by the service command in the same manner as for other civilian employees. Housing and messing facilities are available at Lovell General Hospital (Fort Devens, Mass.) and Lawson General Hospital (Atlanta, Ga.) at the customary charges, but not at Letterman General Hospital (San Francisco). The Adjutant General, the Surgeon General, the commanding general or commanding officer of the general hospital giving the course, and the headquarters of the service command in which the general hospital is located will be furnished a copy of each order issued.

APPETIZING HOSPITAL RATIONS FOR WOUNDED OVERSEAS

The War Department announced recently that a special hospital ration has been developed by the Quartermaster Corps for use in field hospitals overseas which has been made appealing to the eye as well as to the appetite. Sufficient for 25 men for one day, the ration includes a variety of canned fruits, fruit juices, dehydrated soup, coffee, sugar and evaporated milk. Each of the components is packed in a metal container. The complete ration, boxed and marked with the Red Cross insigne, weighs about 60 pounds and is readily transported even to hospitals in the battle zones. The hospital ration was designed to supplement standard field rations ordinarily served wounded men in theaters of operation and to meet the dietary needs of hospitalized soldiers.

ROOMS NAMED IN MEMORY OF BATAAN NURSES AT FINNEY GENERAL HOSPITAL

The nurses' quarters at Finney General Hospital, Thomasville, Ga., have been specially fitted out as a memorial to nurses who performed such noteworthy services in the Philippines, with rooms named for those nurses who were left behind on Bataan at the time of its surrender. Col. Samuel W. Browne, commanding officer of the hospital and a veteran of World War I, who knew many of these nurses personally, had seven plaques made, one for each of the nurses' quarters and bearing five names each, to commemorate the gallant and unselfish service which they gave on Bataan.

PURPLE HEART AND OAK LEAF CLUSTER TO CAPT. JAMES C. LeFON

Capt. James C. LeFon, formerly of Richmond, Va., was recently awarded the Purple Heart and also the Oak Leaf Cluster. He has been wounded twice while performing duties on the front and is at present with the Fifth Army in Italy. Dr. LeFon graduated from the Medical College of Virginia, Richmond, in 1931 and entered the service in June 1942.

ADMINISTRATIVE FUNCTIONS OF SPECIAL PROGRAMS BRANCH TRANSFERRED

The administrative functions of the Special Programs Branch, Supply Service, Office of the Surgeon General, Washington 25, D. C., have been transferred to the Army Medical Purchasing Office, 52 Broadway, New York. The programs under the Special Programs Branch are (1) Optical Program (Spectacles), (2) Artificial Eye Program, (3) Arch Support Program, (4) Books and Journals Program.

ARMY SPECIALIZED TRAINING PROGRAM UNITS

Army Service Forces Circular No. 35 states that the provisions of ASF Circular No. 159, dated Dec. 23, 1943, which provide for instruction in "Control of Malaria and Malaria Discipline" at Army Service Forces schools, are not applicable to Army Specialized Training Program Units.

MISCELLANEOUS

HOSPITALS NEEDING INTERNS AND RESIDENTS

The following hospitals have indicated to the Council on Medical Education and Hospitals that they have not completed their house staff quotas allotted by the Procurement and Assignment Service:

(Continuation of list in THE JOURNAL, February 26, p. 582)

IOWA

Broadlawns Polk County Hospital, Des Moines. Capacity 295; admissions, 3,811. T. P. Sharpnack, Administrator (2 interns—October 1).

NEW JERSEY

Hackensack Hospital, Hackensack. Capacity 250; admissions, 9,353. Mary Stone Conklin, R.N., Superintendent (interns—October).

OHIO

Aultman Hospital, Canton. Capacity 150; admissions, 6,332. James W. Stephan, Director (3 interns).

St. Mary's Hospital, Cincinnati. Capacity 200; admissions, 4,881. Sister Theonilla, Superintendent (3 interns).

PRIORITY RATINGS FOR PAPER CUPS AND CONTAINERS

The executive director of the Paper Cup and Container Institute, New York, stated that because of the acute shortage of paper cups and containers the War Production Board has amended Direction 2, Priorities Regulation No. 3, to include other essential users of paper service. Welfare organizations are permitted under this amendment to apply priority ratings to orders for the feeding of service men and their guests. The amendment also provides for persons engaged in serving passengers on trains and planes. It also enables hospitals to apply priority ratings to orders for serving all patients instead of restricting it to patients in contagious wards and employees, as formerly. Use of hot drink cups for cold food and beverages is prohibited under the amendment, and therefore only hot food and beverages can be served in hot drink cups and containers. By serving cold drinks and food in cold cups and containers, considerable time and paper is conserved, as they require less time to produce and use less paper. The use of paper cups with individual bottled beverages also is prohibited. No persons, except in the case of military exchanges or service departments, may apply for the purchase of paper cups or food containers under blanket MRO ratings if he did not use such cups and containers before Oct. 29, 1943. However, plants, hospitals and concessionaires desiring to open new "in plant" feeding operations may apply for preference ratings to obtain supplies of paper cups and food containers on form WPB-541 which formerly was PD-IA. The amendment order dated Jan. 29, 1944 will continue until May 1, 1944 unless previously extended.

MEDICAL NEGLECT AMONG NETHERLANDS WORKERS FORCED TO LABOR IN GERMAN WAR PLANTS

Recent reports from the Netherlands Information Bureau indicate that many Netherlands workers forced to labor in German war plants have been stricken with dysentery, scarlet fever and typhus. The report stated that there is a serious shortage of doctors in the reich. A Dutch student in Germany published in the Dutch underground paper *DeGeus* (the Beggar) the conditions prevailing in a factory employing 14,000 Netherlands, Polish and Russian workers, in which he stated that one woman doctor was delegated to look after the physical well-being of these 14,000, but that she actually gave but one hour of her time each week for consultations. Three male nurses, however, were on duty every day at this factory who scarcely knew the rudiments of first aid. Whenever these male nurses were unable to cope with an emergency the patient would be sent to a nearby town which had two doctors for its 80,000 inhabitants, the patient often waiting a week or two before being hospitalized. Scarlet fever and diphtheria patients were often placed in wards side by side, with the result that most patients caught both diseases, and instruments were repeatedly used without being sterilized.

LOWER NAVY REQUIREMENTS SET BY MEDICAL BOARD

The special five man medical commission (THE JOURNAL, January 15, p. 166) which President Roosevelt appointed to study physical, mental and moral standards for admission to the armed forces has submitted to the White House a report which recommends that navy eye and teeth requirements be lowered to correspond to those in army general service requirements. The move is expected to have little immediate effect on the nation's three million 4-F's but will improve the general selective service picture by allowing more men to enter the Navy and enabling Selective Service to place more men where they are needed most. It was learned that Selective Service officials have seen the report and that, as a result of its recommendations, the reexamining of a number of 4-F's will be required.

STEEL SCREEN CLOTH FOR CIVILIANS

The War Production Board announced recently that preference ratings of AA-3 or less on civilian purchase orders for steel insect screen cloth are to be disregarded, to provide equitable distribution of this product for civilian use. Such purchase orders are now to be treated as unrated orders. Production of this type of steel screen cloth for civilian use is now at the rate of half of normal yearly production. To effect equitable distribution of this limited output, order L-303 (issued Dec. 13, 1943) required producers to supply civilian needs without regard to the customers' size, location or affiliated outlets. However, some orders carry preference ratings of AA-3 or less and some are unrated, and it was found that this situation seriously interfered with the distribution required by the order. The amendment, issued and effective February 10, remedies this difficulty by placing all civilian purchase orders on the same footing, irrespective of whether they were originally rated AA-3 or less, or unrated.

NEW SYMBOLS FOR WAR GASES

The Chemical Warfare Service of the Office of Civilian Defense, Washington, D. C., recently adopted new symbols for certain chemical warfare agents and instituted symbols for several war gases which previously had no designation. A list of the agents concerned is given herewith with the old and new symbols:

Chemical Warfare Agents	Symbols	
	Old	New
Lewisite	M-1	L
Mustard	HS	H
Mustard-lewisite mixture	MS	HL
Brombenzylcyanide	CA	BBC
Phenyldichlorarsine	PDA	PD
Arsine		SA
Cyanogen chloride		CC
Hydrogen cyanide		AC
Nitrogen mustard		HN

DR. WINFORD H. SMITH IS CHAIRMAN OF MEDICAL SUPPLIES COMMITTEE

The combined Production and Resources Board recently announced the appointment of Dr. Winford H. Smith as American member and chairman of its Medical Supplies Committee. Dr. Smith has been director of Johns Hopkins Hospital, Baltimore, for more than thirty years.

NINTH CIVILIAN DEFENSE REGION

Dr. Ludwig A. Emge, former executive and professor of obstetrics and gynecology, Stanford University School of Medicine, San Francisco, is now serving as Senior Surgeon (R), United States Public Health Service, and has been appointed regional medical officer of the Ninth Civilian Defense Region, Office of Civilian Defense, effective as of Jan. 1, 1944.

ORGANIZATION SECTION

OFFICIAL NOTES

THE CHICAGO SESSION

Railroad and Hotel Reservations

Physicians who expect to attend the annual session of the American Medical Association to be held in Chicago June 12 to 16 should make hotel reservations at the earliest possible time. The demand for hotel accommodations in Chicago is very great. Accommodations can rarely be found unless reservations have been made. A list of Chicago hotels with room rates will be found from time to time in the advertising pages of THE JOURNAL, together with a blank form that can be torn out and used for the purpose of applying for hotel reservations. In asking for reservations the hotel of first, second and third choice should be indicated and the kind of accommodations desired should be definitely stated.

While reservations of railroad accommodations cannot be made more than thirty days in advance, it is highly important that such reservations should be made at the earliest possible time and that whenever possible return pullman accommodations should be reserved at the time transportation is purchased at the home station. It may be very difficult to secure return pullman reservations for the desired time after reaching Chicago. In those instances in which return pullman accommodations cannot be secured at the time transportation is purchased at the home station, such accommodations should be applied for at the earliest possible moment after reaching Chicago.

Chicago hotels have many reservations made months in advance, and it may be that in some instances physicians who make hotel reservations for a specified time during the Chicago session will encounter difficulty in retaining their hotel rooms after the time for which their own hotel accommodations have been reserved.

DOCTORS AT WAR

Radio broadcasts of Doctors at War by the American Medical Association in cooperation with the National Broadcasting Company and the Medical Department of the United States Army and the United States Navy are on the air each Saturday at 4:30 p. m. Eastern war time (3:30 Central war time, 2:30 Mountain war time and 1:30 Pacific war time).

The titles and guest speakers for the next three programs are as follows:

March 4. "New Life Preserver."
Speaker, Capt. W. M. Craig (MC), U.S.N.R.

March 11. "Battles Won in Laboratories."
Speaker, A. C. Ivy, Ph.D., M.D., Northwestern University.

March 18. "You Must Help Win This War."
Speaker, Harold A. Vonachen, M.D., Medical Director, Caterpillar Tractor Company, Peoria, Ill.

THE REVENUE ACT OF 1943

PREPARED BY THE BUREAU OF LEGAL MEDICINE AND LEGISLATION

The Revenue Act of 1943 has become a law over the veto of the President. The changes it effects will be applicable to 1944 incomes, and taxpayers must take those changes into consideration when filing their declarations of estimates for 1944 taxes. The date before which these declarations must be filed has been extended from March 15 to April 15. The new law has no effect on the tax due on 1943 income, and physicians may rely on the statement published in THE JOURNAL, January 29, for aid in filing the final return for 1943.

Allowances for Dependents and Marital Status.—The new act leaves unchanged the basic tax rates and the credit for marital status and for dependents. Taxpayers may no longer, however, apportion the personal exemption and credit for dependents where a change in status occurs during the year. The new act provides that allowances for personal exemption and dependents must be based on the status of the taxpayer as of July 1. Since the declaration of estimate of tax must be filed by April 15, the status as of that date will initially be determinative. If the status changes before July 1, a revised declaration must be filed to take into consideration the change.

Victory Tax.—The method of determining the victory tax has been modified. Under the previous law that tax was 5 per cent of victory tax net income with a credit allowance dependent on the taxpayer's marital or head of family status. This has been changed so that the rate is a flat 3 per cent of the victory tax net income in excess of $624 regardless of family status and with no credit allowance.

Earned Income Credit.—The credit of 10 per cent for earned income has been abolished. This change will result in a slight increase in the tax due by the individual taxpayer, but the increase in no case will exceed $84.

Deductibility of Excise Taxes.—Formerly the taxpayer was permitted to deduct certain excise taxes, such as taxes on theater tickets, use tax on automobiles and boats, stamp taxes, taxes on club dues, telephone calls and so on. Such deductions may still be claimed in connection with taxes for 1943 but are not permitted in connection with the declaration of estimate for 1944 taxes. If any of the excise taxes, however, fall in the category of trade or business expenses or are necessitated in connection with the production or collection of income or the management, conservation or maintenance of property held for the production of income they may still be deducted.

Special Deduction for the Blind.—A special deduction of $500 for blind persons is authorized. A blind person is defined as one whose central visual acuity does not exceed 20/200 in the better eye with correcting lenses or whose visual acuity is greater than 20/200 but is accompanied by a limitation in the fields of vision such that the widest diameter of the visual field subtends an angle no greater than 20 degrees. Status for the deduction will be determined as of July 1 of the taxable year.

Underestimated Tax.—The penalty for substantially underestimating taxes has been modified in several respects. As the change applies to the declaration to be filed on or before April 15, if the taxpayer bases his estimate on anticipated income as large as his 1943 income, no penalty attaches even though the final return for 1944, to be filed on or before March 15, 1945, discloses a substantial underestimate.

Returns by Exempt Organizations.—Many organizations exempt from the payment of income taxes under section 101 of the Internal Revenue Code will be required to file annual returns with the Bureau of Internal Revenue. This requirement is applicable to taxable years beginning after Dec. 31, 1942. The date before which such returns must be filed is not fixed in the law. It is not contemplated that such exempt organizations will be taxed at the present time, but the informational return must contain the items of gross income, receipts and disbursements, and such other information as the Commissioner of Internal Revenue, with the approval of the Secretary of the Treasury, may by regulation prescribe. Such organizations too must keep such records, render under oath such statements, make such other returns and comply with such

rules and regulations as the commissioner with the approval of the secretary, may from time to time prescribe.

No such annual return need be filed by any organization exempt from taxation under the provisions of section 101—

(1) which is a religious organization exempt under section 101 (6); or

(2) which is an educational organization exempt under section 101 (6), if such organization normally maintains a regular faculty and curriculum and normally has a regularly organized body of pupils or students in attendance at the place where its educational activities are regularly carried on; or

(3) which is a charitable organization or an organization for the prevention of cruelty to children or animals exempt under section 101 (6), if such organization is supported in whole or in part by funds contributed by the United States or any state or political subdivision thereof or is primarily supported by contributions of the general public; or

(4) which is an organization exempt under section 101 (6) if such organization is operated, supervised or controlled by or in connection with a religious organization entitled to exemption under that section; or

(5) which is an organization exempt solely under section 101 (3), relating to fraternal beneficiary societies, orders or associations; or

(6) which is an organization exempt under section 101 (15) if such organization is a corporation wholly owned by the United States or any agency or instrumentality thereof, or a wholly owned subsidiary of such a corporation.

Social Security Taxes.—The tax on employers and employees under the Federal Insurance Contributions Act will remain at 1 per cent until Jan. 1, 1945.

Increase in Postal Rates.—The new act increases for the duration of the war and for six months thereafter certain postal rates. These increases will become effective thirty days after the enactment of the act (February 25). The rate on first class mail for local delivery is changed from 2 cents to 3 cents per ounce, on air mail from 6 cents to 8 cents per ounce, for money orders from 6-22 cents per order (depending on the amount) to 10-37 cents an order, on registered mail from 15 cents-$1 per article to 20 cents-$1.35 per article, on insured mail from 5-35 cents per article to 10-70 cents per article and on C. O. D. mail from 12-45 cents per article to 24-90 cents per article. Furthermore the rate on fourth class mail will be increased by an amount equal to 3 per cent of the previous rate, or by 1 cent, whichever is the greater. If the 3 per cent amount results in a fraction or part of a cent, such fractional part will be disregarded unless it amounts to one-half cent or more, in which case it will be increased to 1 cent.

MEDICAL LEGISLATION

MEDICAL BILLS IN CONGRESS

Changes in Status.—H. R. 149 has passed the House and Senate, proposing to fix a reasonable definition and standard of identity of certain dry milk solids. H. R. 3687, the Revenue Act of 1943, has become a law over the veto of the President. It repeals the earned income credit, provides a special deduction of $500 for blind persons, freezes the tax on employers and employees under the Federal Insurance Contributions Act at 1 per cent until Jan. 1, 1945, changes the method of determining the victory tax by establishing a flat rate of 3 per cent with no credit allowance, denies the deductibility of certain federal excise taxes, imposes on many organizations exempt from the income tax law the duty of filing annual information returns and effects other changes that taxpayers must take into consideration in filing their declarations of estimated tax on or before April 15.

Bills Introduced.—S. 1726, introduced by Senator Davis, Pennsylvania, proposes an appropriation of $5,000,000 to enable the Administrator of Veterans' Affairs to provide seeing-eye dogs for blind veterans who are entitled to disability compensation under the laws administered by the administrator. H. J. Res. 241, introduced by Representative Judd, Minnesota, would request the President to approach the governments of opium-producing countries throughout the world, urging on them in the interest of protecting American citizens and those of our allies and of freeing the world of an age-old evil, that they take immediate steps to limit and control the growth of the opium poppy and the production of opium and its derivatives to the amount actually required for strictly medicinal and scientific purposes. H. R. 4270, introduced by Representative Brooks, Louisiana, proposes an appropriation of $3,000,000 to construct a veterans' hospital in northwest Louisiana, near Shreveport, for the accommodation of approximately 2,000 bed patients.

STATE MEDICAL LEGISLATION

New Jersey

Bills Introduced.—S. 101 proposes so to amend the uniform narcotic drug act as to include "isonipecaine" within the definition of a narcotic drug. The bill proposes specifically to define isonipecaine as "the substance identified chemically as 1-methyl-4-phenyl-piperidine-4-carboxylic acid ethyl ester, or any salt thereof by whatever trade name identified." A. 61 proposes to provide for the establishment and administration of a plan for providing compensation to covered workers to be paid them when they lose time from work because of sickness.

New York

Bills Introduced.—S. 867 proposes to authorize a temporary state commission to "make such studies, surveys and investigations as it may deem necessary and proper in connection with the proposal to the governor and the legislature of programs for medical care for persons in the state of New York and to make such proposals." S. 868 proposes to continue to March 31, 1945 the temporary state commission created by chapter 682 of the laws of 1938 to formulate a long-range state health program. A. 1303, to amend the public health law in relation to the examination or quarantine of persons suspected of venereal disease, proposes that if any such infected person refuses to submit to the required examination or to permit specimens of blood or bodily discharges to be taken for laboratory examination or to comply with the restrictions imposed by quarantine the appropriate health officer may apply to a justice of the supreme court or a county judge for an order compelling compliance. The bill also proposes to authorize the local or district state health officer to require any person within his jurisdiction who is found to be infected with a venereal disease in a state which is or may become communicable to submit to such treatment or quarantine, or both, as may be necessary to terminate the communicable stage.

Virginia

Bills Introduced.—S. 219, to amend the laws relating to venereal diseases, proposes (1) to require health officers to investigate all cases of lymphogranuloma inguinale or granuloma inguinale, as well as syphilis, gonorrhea and chancroid, as the present law provides, within their territorial jurisdiction; (2) to authorize health officers to require persons suspected of being infected with any of the venereal diseases just mentioned to submit to examination; and (3) to make it a misdemeanor for any person found infected with any of the venereal diseases mentioned to fail or refuse to take the treatment prescribed by a competent physician or to fail to continue a treatment until cured. S. 234 proposes to prohibit the retail sale or distribution, except on the prescription of a doctor of medicine, dentist or veterinarian, of hormones, or hormone drug preparations, whether of natural origin, prepared from the so-called glands of internal secretion or endocrine glands, or whether synthetically produced, by whatsoever trade name or designation, or any compound or mixture thereof.

Bill Passed.—H. 271 passed the House of Delegates, February 24, proposing so to amend the medical practice act as to provide that the board of medical examiners consist of nine regular physicians, one homeopath and one osteopath.

Medical News

(PHYSICIANS WILL CONFER A FAVOR BY SENDING FOR THIS DEPARTMENT ITEMS OF NEWS OF MORE OR LESS GENERAL INTEREST: SUCH AS RELATE TO SOCIETY ACTIVITIES, NEW HOSPITALS, EDUCATION AND PUBLIC HEALTH.)

ALABAMA

Personal.—Dr. William D. Lyon has resigned as pediatric consultant to the bureau of maternal and child health of the state department of health to enter private practice in Andalusia.

Birmingham Chosen for New Medical Site.—Birmingham has been selected as the site for the new Medical College of Alabama, to operate as a part of the University of Alabama, University. Committees have been working on the selection of the proper site since the enactment of a bill last year which appropriates a million dollars for land, buildings and equipment and $366,750 for each of the fiscal years ending Sept. 30, 1944 and Sept. 30, 1945 (THE JOURNAL, June 26, p. 629). On January 21 newspapers reported that Birmingham offered the state the Hillman Hospital in addition to an adjacent tract of land.

CALIFORNIA

Dr. Markee Goes to North Carolina.—Joseph E. Markee, Ph.D., professor of anatomy, Stanford University School of Medicine, San Francisco, has been made professor and head of the department of anatomy at Duke University School of Medicine, Durham, N. C. Dr. Markee received his doctor of philosophy degree at the University of Chicago in 1929 and has been associated with Stanford since that time.

FLORIDA

Dr. Sowder Transferred to War Shipping Administration.—Wilson T. Sowder, P. A. Surg., U. S. Public Health Service, who had been lent to the state board of health to serve as acting director of the bureau of local health service, has been transferred to the War Shipping Administration. Newspapers report that he will be venereal disease control officer for the merchant marine service.

INDIANA

Milk Produce Cause of Typhoid Epidemic.—Cheese or butter produced by the Sanitary Dairy Company of Peru is said to be the cause of the typhoid epidemic in north central Indiana which involved at least 175 cases of the disease and six deaths. In a statement to the press, Dr. Thurman B. Rice, Indianapolis, acting state health director, stated that no responsibility for the epidemic is attached to the present owners of the company who took possession January 1 and who have not made any butter or cheese since that date. It was stated that the original source of the typhoid bacillus may have been a carrier working in the plant or supplying the plant. The suspected products were sold under the trade names of "Sanitary Cheese" or "Peru Sanitary Butter." Persons who have cheese or butter in their iceboxes that would come under the present description should determine from their grocer whether the product may have come from this company. If so, it should be destroyed. Grocers and meat dealers who may have any of this butter or cheese on their counters are ordered not to sell it.

KENTUCKY

Dr. Pritchett Named President of State Association.—Dr. James H. Pritchett, Louisville, was recently elected by the council of the Kentucky State Medical Association as president of the association to succeed the late Dr. Van A. Stilley, Benton. Dr. Pritchett is associate clinical professor of pediatrics at the University of Louisville School of Medicine.

MICHIGAN

Personal.—Dr. Douglas H. Fryer, formerly director of the Bay City-County Health Department, is now field medical director and assistant director of the bureau of local health services of the Michigan Department of Health, Lansing.—— Dr. Ivor D. Harris has been appointed acting director of the department of radiology at Wayne University College of Medicine, Detroit. Dr. John C. Kenning, director of the department, is on leave of absence on account of ill health. During Dr. Kenning's absence Dr. Harris holds the rank of instructor in radiology.

Physician Convicted for Conspiracy to Spy.—Dr. Fred William Thomas, Detroit, was convicted February 24 by a federal court jury of conspiracy to spy for Germany, newspapers report. Dr. Thomas was accused with seven others of conspiring to obtain information to be transmitted to Germany. Six co-defendants pleaded guilty. A seventh was discharged. In the case of Dr. Thomas, the jury recommended leniency, it was stated. Government attorneys had not asked for imposition of the death penalty, and the maximum imprisonment possible under the statute would be thirty years.

MINNESOTA

Red Cross, Military Personnel and Civilians Cooperate in Hospital Strike.—Red Cross, local military personnel and civilian volunteers cooperated in caring for patients at the University of Minnesota Hospitals, Minneapolis, in January when service employees of the university went on strike. On January 14, the day after the strike was called, 46 civilian patients were discharged, and 14 army patients transferred to the station hospital at Fort Snelling. Three patients, considered as "acute emergencies," were admitted to the hospital during the day. On January 15, nine service employees of the hospital were on duty out of a normal staff of more than 150. An army cook on leave volunteered his services and, with navy cooks and civilian volunteers, prepared the meals for the patients. Red Cross aides assisted in the preparations for cooking and serving meals. It was announced, January 16, that members of the Public Building Service Employees Union 113, which had declared the strike against the university, had recommended that hospital employees return to their work. This was accomplished and the following day reports indicated that the maintenance of the hospital was operating along normal lines. On January 20, after an agreement between the union and the board of regents of the university, newspapers announced that the functioning of the university was proceeding smoothly.

Licenses Revoked.—The Minnesota State Board of Medical Examiners on Dec. 16, 1943 revoked the license to practice medicine of Dr. Walter D. Hammond, Minneapolis. The physician had been charged with "immoral, dishonorable and unprofessional conduct" in that he permitted two unlicensed persons, A. A. Morgan and C. C. Morgan, associated with him in the practice of medicine at the Health Institute, 106 Washington Avenue South, Minneapolis, to examine, diagnose and render treatment to one Ernest Anderson, Hastings. The patient died on Aug. 24, 1943 of malignant teratoma of the testicle with pulmonary metastasis. Dr. Hammond was also charged with having failed to take the necessary and proper steps to diagnose the ailment correctly and with failing to render proper treatment for the condition. It was also alleged that "a grossly exorbitant fee of approximately $1,250" was charged Anderson, including $485 for "capsules which were of no value whatsoever" in the treatment of cancer. It was also alleged that because of the unlawful and dishonorable conduct on the part of Dr. Hammond "every chance for the ultimate recovery" of the patient was destroyed. At the hearing Dr. Hammond admitted that he had examined Anderson but denied making a diagnosis of "hydrocele," which had been the diagnosis rendered at the institute, it was stated. He also claimed that he had seen Anderson on only one occasion. He admitted that he had been associated for a number of years with the two Morgans but disclaimed responsibility for their acts. He further testified that he neither owned the Health Institute nor did he pay rent on the space occupied by him. On cross examination he admitted that he received only such share of the proceeds of the Health Institute as was allotted to him by the Morgans. During the investigation and prior to the hearing, A. A. Morgan committed suicide.——On Dec. 16, 1943 the Minnesota State Board of Medical Examiners also revoked the license to practice medicine of Dr. O. H. Bakke, Minneapolis. Dr. Bakke's license had been suspended April 10, 1943, for a period of five years for issuing 136 narcotic prescriptions to 4 persons. Notwithstanding the fact that Dr. Bakke has no lawful right to continue to practice medicine, an investigation by the Federal Bureau of Narcotics and the Minnesota State Board of Medical Examiners disclosed that Dr. Bakke was continuing to practice medicine from his home and had issued 4 narcotic prescriptions to one G. F. Lambert between Oct. 24 and Nov. 1, 1943. There was also evidence that Dr. Bakke, three days before the board hearing, issued a narcotic prescription to another person.

MISSOURI

Dr. Barry Wood Ill with Typhus.—Dr. William Barry Wood Jr., Clayton, Busch professor of medicine and head of the department at Washington University School of Medicine, St. Louis, is reported to be convalescing from endemic typhus. According to the St. Louis *Post-Dispatch*, Dr. Wood is one of two persons reported to be ill with the disease in St. Louis. It was stated that both contracted the mild murine form of typhus.

Physician Sentenced for Illegal Narcotics Sale.—Dr. Fred A. Stahl, Springfield, was sentenced to two years in prison in federal court, January 28, newspapers report. Judge Albert L. Reeves declared that the sentences on the two counts on which the physician was convicted by a jury January 26 for the illegal sale of morphine were to run concurrently. Defense Attorney William L. Vanderventer immediately gave notice of appeal and was allowed ninety days in which to complete all filings. Dr. Stahl graduated at Harvard Medical School, Boston, in 1921.

NEW YORK

Dr. Craig Retires from State Service.—Dr. Walter J. Craig, Albany, director of the division of orthopedics of the state department of health, has retired from state service, effective February 1, to devote his entire time to the private practice of orthopedic surgery. He joined the state department of health in 1927 as orthopedic surgeon, becoming director of the division the following year.

New York City

License Reinstated.—The license of Dr. Samuel H. Kauffman, Brooklyn, revoked Nov. 23, 1933, has been reinstated by the state board of medical examiners, effective February 3.

New Administrator Named for Hospital Department.—Mr. Harry Sesan, vice president, Associated Hospital Service of New York, has been named in charge of the administrative activities of the hospital department of the service. He succeeds the late Dr. Paul Keller.

Annual Graduate Fortnight.—"Infections and Their Treatment" will be the theme of the annual graduate fortnight of the New York Academy of Medicine, October 9-20. Special emphasis will be placed on the more recent chemotherapeutic agents. The fortnight, as in the past, will include morning panel discussions, afternoon hospital clinics, evening lectures and pathologic demonstrations. There will also be a scientific exhibit, including the more recent pharmaceuticals and an appropriate library exhibit. Additional information may be obtained from the Committee on Medical Education, New York Academy of Medicine, 2 East 103d Street, New York 29.

NORTH CAROLINA

Personal.—Dr. William Ross Cameron, Portsmouth, Va., has been appointed health officer for Charlotte, effective March 1.——Dr. John L. B. Ward, Asheville, has been elected a member of the state board of medical examiners to fill the unexpired term of the late Dr. Lewis W. Elias, Asheville.

Winners of Student Awards.—Dr. William W. Shingleton in the Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, was awarded first prize of $25 in a group of prizes inaugurated recently by the *Journal* of the Bowman Gray School of Medicine in its effort to recognize outstanding student papers. The title of Dr. Shingleton's paper was "The Etiological Aspects of Hyperthyroidism," published in the September issue of the *Bowman Gray Journal*. Second prize of $15 went to Robert R. King Jr., fourth year student, for his work on "The Preclinical Student and Oncology," published in the March issue, and third prize to Dr. Moses Edward Rice Jr., for his paper on "A Physiological Interpretation of the Clinical Changes in Sprue," published in the November issue. The prizes are to be awarded annually, the selections to be made by a group of judges representing members of the medical school faculty.

OHIO

Morris Memorial Lecture.—Dr. Louis Hamman, associate professor of medicine, Johns Hopkins University School of Medicine, Baltimore, will deliver the Roger S. Morris Memorial Lecture, March 7, in the auditorium of the University of Cincinnati College of Medicine. His subject will be "The Diagnostic Implications of Aortic Insufficiency."

OKLAHOMA

Changes in the Faculty.—Arthur A. Hellbaum, Ph.D., associate professor of physiology, University of Oklahoma School of Medicine, Oklahoma City, has been named professor of pharmacology and acting chairman of the department. Dr. John W. Cavanaugh, who was recently appointed assistant professor of surgery, has now been named full time professor of surgery at the medical school.

PENNSYLVANIA

Personal.—Dr. James D. Lewis, Scranton, has been appointed health director of Lackawanna County, succeeding Dr. William T. Davis, Scranton.

Philadelphia

Charles Jenks Pilling Dies.—Charles Jenks Pilling, president of the George P. Pilling and Son Company, died February 1.

Hospital News.—A urology room has been added to the surgical suite of the Hospital of the Woman's Medical College of Pennsylvania through a gift of Mr. William Goldman. Under the supervision of the department of urology, the new unit is outfitted with modern surgical and x-ray equipment for both diagnostic and therapeutic procedures and for teaching.

Physician Creates Hospital Memorial.—Dr. Louis Schwarz, who died December 17 in Mount Sinai Hospital, where he had maintained a residence since ill health forced his retirement in 1936, bequeathed to the hospital his $45,000 estate. The fund will be known as the Albert and Nanni Schwarz Memorial Fund of Mount Sinai Hospital and will be a memorial to the parents of Dr. Schwarz.

Dr. Pearson Resigns as Medical Dean.—Dr. William A. Pearson has resigned as dean of Hahnemann Medical College and Hospital of Philadelphia, a position he held since 1913. Dr. Pearson will continue as professor and head of the department of chemistry. William G. Schmidt, Ph.D., has been named acting dean. Dr. Pearson graduated at Hahnemann in 1915. He had been named professor of chemistry in 1906.

Personal.—Dr. Josephine C. Lawney, dean of the Woman's Christian Medical College and medical director of the Margaret Williamson Hospital in Shanghai before the beginning of the war with Japan, was a guest of the Woman's Medical College of Pennsylvania recently. Dr. Lawney returned to the United States on the S. S. *Gripsholm* in December.——Dr. Hobart A. Reimann, Magee professor of practical medicine and clinical medicine, Jefferson Medical College of Philadelphia, visited Puerto Rico in December as guest of the Puerto Rico Medical Association in San Juan, where he gave several lectures on acute infectious diseases.

TENNESSEE

Personal.—Dr. Solomon J. Axelrod has resigned as director of the division of preventable diseases of the Chattanooga and Hamilton County Department of Health to accept a commission as passed assistant surgeon in the U. S. Public Health Service.——Dr. William L. Phillips, who was recently placed on inactive duty after seventeen months in the army medical corps, has been named director of the Obion-Lake health district. He succeeds Dr. George W. James, who, it is reported, has accepted a position with the New York State Department of Health.

TEXAS

Personal.—Lewis C. Robbins, P. A. Surgeon, U. S. Public Health Service Reserve, formerly health officer of Wichita Falls, was presented with the distinguished service award of the United States Junior Chamber of Commerce on January 14. Dr. Robbins was cited for his successful conduct of a venereal disease control campaign that he instituted in Wichita Falls. He is now associated with the public health department in San Antonio.——Dr. Joe D. Nichols was chosen president of the Atlanta Chamber of Commerce, January 14.

Dr. Stuart Wallace Chosen Recipient of New Professorship.—Dr. Stuart A. Wallace, chairman of the department of pathology, Baylor University College of Medicine, Houston, is the first incumbent of the newly created Fulbright professorship of pathology. The professorship was endowed at Baylor University under a contract executed between Mrs. Irene Fulbright, widow of R. C. Fulbright of Houston and Washington, and the Houston executive committee of the board of trustees of Baylor University (THE JOURNAL, February 26, p. 587).

University News.—Frank M. Stead, Ph.D., associate professor of sanitation, University of Texas School of Medicine, Galveston, has resigned to take charge of studies on industrial hygiene for the California State Department of Public Health at Berkeley. Joe B. Winton has been appointed associate professor of sanitation to succeed Dr. Stead. J. Allen Scott, Sc.D., senior statistician in the division of vital statistics of the United States Bureau of Census and formerly with the Rockefeller Foundation in Egypt, has been appointed as associate professor of preventive medicine in the special field of statistics and epidemiology.

UTAH

Physician Honored. — Dr. Preston G. Hughes, Spanish Fork, was awarded the distinguished service award, January 19, at the annual banquet, honoring the young man of junior chamber of commerce age who renders the most notable civic service during the year. In presenting the award John E. Booth, chairman of the committee, stated that Dr. Hughes had given freely of his time and energy in examining local inductees at the local service board as well as making a number of other contributions to civic service.

WEST VIRGINIA

Changes in Health Officers.—Dr. Ward L. Oliver, Cobleskill, N. Y., has been appointed health director of district 3 with headquarters at Point Pleasant. He succeeds Blinn A. Buell, Surgeon, U. S. Public Health Service, who has been transferred to another state. The district is composed of Jackson, Mason, Putnam and Roane counties. —— Dr. John W. Gilmore, Wheeling, has been named director of the city-county health department in Wheeling to succeed Dr. Andrew J. Niehaus, resigned.

Dr. Gerhardt Named to Head New Cancer Control Division.—Dr. Paul R. Gerhardt, director of the bureau of medical services in the department of public assistance at Charleston, has been appointed by Dr. John E. Offner, state health commissioner, as director of the new division of cancer control. The appointment was made under the provisions of an act passed at the 1943 session of the legislature. The act authorizes the commissioner to appoint the director in consultation with the public health council. The division is authorized to set up cancer diagnostic and treatment clinics in hospitals meeting certain standard minimum requirements. In the establishment and operation of such clinics the division is to consult and cooperate with the West Virginia State Medical Association. Free diagnostic service and treatment are to be furnished needy patients within the limits of funds available for the purpose. The bill creating the division was signed March 19, 1943. With the appointment of Dr. Gerhardt as director, it is now thought that the division will be in full operation within a few weeks. An appropriation of $50,000 per annum for the use of the division was made by the legislature in 1943. Dr. Gerhardt has served as head of the bureau of medical services for the past two years. As such he has directed the department programs for crippled children and adult physical rehabilitation. Prior to that time he was engaged in industrial practice at Van, Boone County. He is a graduate of the University of Wisconsin Medical School, Madison, and was licensed in West Virginia in 1938.

WISCONSIN

Personal.—Dr. Willard C. Sumner was recently appointed health officer of Edgerton, succeeding Dr. George F. Burpee, who entered the navy.——Dr. George D. Reay, Onalaska, has been appointed coroner of La Crosse County and Dr. Lewis A. Moore has been named health officer of Monroe to succeed Dr. Clarence E. Baumle, who resigned, effective January 1.

Meeting of Trudeau Society.—The Wisconsin Trudeau Society will meet at the Lake View Sanatorium, Madison, March 11. Among the speakers will be:

Dr. Earl E. Carpenter, Hawthorne, Respiratory Hazards of Electric Welding.
Dr. Allan A. Filek, Madison, Case Finding Among Industrial, Non-industrial and Institutional Groups.
Dr. Florence E. MacInnis, Milwaukee, Significant Data on Tuberculosis in Milwaukee During 1943.
Dr. Kenneth G. Bulley, Aurora, Ill., Short Term Pneumothorax.
Dr. Frank L. Jennings, Indianapolis, Aims and Accomplishments of American Trudeau Society Committee on Undergraduate Medical Education.
Dr. James M. Wilkie, Madison, Thoracoplasty in Some Advanced Cases of Tuberculous Bronchitis.
Dr. David D. Feld, Wauwatosa, Significance of Tubercle Bacilli in Fasting Gastric Contents.
Dr. Helen A. Dickie, Madison, Some Problems in the Differential Diagnosis of Pulmonary Tuberculosis and Atypical Pneumonia.

Dr. John D. Steele Jr., Milwaukee, is secretary of the Wisconsin Trudeau Society.

ALASKA

New Secretary of Medical Board. — Dr. William M. Whitehead, Juneau, has been appointed to the Alaska Board of Medical Examiners and elected secretary-treasurer to fill the vacancy created by the death of Dr. Walter W. Council, who at the time of his death on Nov. 13, 1943 was the secretary-treasurer. Dr. Leonard P. Dawes, Juneau, is president of the board, and other members are Drs. LeRoy W. Flora, Anchorage; Arthur J. Schaible, Fairbanks, and Thomas Morcom, Nome. Regular meetings of the board for examinations are held on the first Tuesday of March and the first Tuesday of September each year at Juneau.

HAWAII

Personal.—Dr. C. Alvin Dougan, Honolulu, has resigned as director of the tuberculosis bureau of the Territory of Hawaii Board of Health, newspapers report. He had held the position for ten years.——Dr. Aaron Sumner Price, New York, has been appointed director of laboratories at the Queen's Hospital, Honolulu.

GENERAL

Election of Officers.—Dr. Cobb Pilcher, Nashville, Tenn., was named president-elect of the Society of University Surgeons at its meeting in Nashville, February 12, succeeding Lieut. Col. Franklin E. Walton, M. C., U. S. Army. Dr. Alexander Brunschwig, Chicago, was installed as president of the society. Dr. Frederick E. Kredel, Charleston, S. C., was chosen treasurer to succeed Dr. Pilcher. The 1945 meeting will be held in New York.

Outwitting Handicaps.—Copies of *Outwitting Handicaps*, a bimonthly magazine intended to assist in the rehabilitation of the handicapped, have recently been made available to military and veterans' hospitals in the United States. The publication presents ideas and suggestions by persons handicapped themselves to assist others in overcoming physical disabilities. The publication is the official organ of "We, The Handicapped, Inc.," a noncommercial fraternal publication founded on the law of human helpfulness. Harry Ernest Smithson is the editor, and Rose D. Meyer associate editor. The address is 15327 Welland Avenue, Detroit 21.

First Ciba Award.—The first Ciba Award, established for outstanding work in endocrinology, is now available. The prize of $1,200 was established by the Ciba Pharmaceutical Company in 1943, the selection of the recipient to be made by the Association for the Study of Internal Secretions. It will be given to an investigator in the field of endocrinology, not more than 35 years of age, whose work may be in the field of either preclinical or clinical endocrinology. If the recipient should choose to use the award toward further study in a laboratory other than that in which he is at present working, the award will be increased to $1,800. The option is left entirely to the recipient. Nominations for 1944 are now invited and should be sent in as soon as possible to Dr. Henry H. Turner, 1200 N. Walker Street, Oklahoma City. They should be accompanied by a list of publications and five reprints if possible.

The Richard Pearson Strong Medal.—On February 28 the first award of the Richard Pearson Strong Medal was made to the man for whom it was named, Dr. Strong, professor of tropical medicine emeritus, Harvard Medical School, Boston. Presentation of the first award was made by Rear Admiral Edward R. Stitt (MC) retired, former surgeon general of the U. S. Navy. The award was established by the Winthrop Chemical Company and will be presented through the American Foundation for Tropical Medicine. It will consist of a palladium medal and a cash honorarium of $500. The medal will bear the name and profile of Dr. Strong, who has devoted his career to tropical medicine. Dr. Strong, who graduated at Johns Hopkins University School of Medicine, Baltimore, in 1897 was in 1899 appointed president of the first board for the investigation of tropical diseases in the Philippine Islands and shortly afterward organized the Philippine Government Biological Laboratory in Manila. In 1907 he was appointed professor of tropical medicine at the University of the Philippines College of Medicine and Surgery, a position he held until 1913, when he joined Harvard Medical School in a similar capacity, holding the latter appointment until 1938, when he became emeritus professor. In 1941 Dr. Strong was appointed consultant to the Secretary of War on tropical medicine and at present is on active duty as colonel, medical corps, Army of the United States, director of tropical medicine at the Army Medical School, Washington, D. C., in charge of the instruction of medical officers in tropical medicine.

Cushing Society Publishes Journal.—The Harvey Cushing Society, which recently extended its membership to become a national organization for neurologic surgeons, has begun the publication of a journal to be known as the *Journal of Neurosurgery*. Number one will appear with the February issue. Dr. Louise C. Eisenhardt, New Haven, Conn., will be the managing editor. The editorial board will be composed of Dr. Gilbert Horrax, Boston, chairman; Capt. Winchell M. Craig (MC), U. S. Naval Reserve, Dr. Kenneth G. McKenzie, Toronto, Ont., Lieut. Col. Roy Glenwood Spurling, M. C., A. U. S., and Dr. A. Asenjo, Santiago, Chile. The first meeting of the Harvey Cushing Society was in 1932. Originally organized by pupils and close associates of the late Dr. Cushing, the organization a few years ago changed its constitution and by-laws to permit the admission of members throughout the country who are interested in neurologic surgery and who have been recognized by the specialty boards. Membership has been designated corresponding, honorary and active, the last group to consist of neurologic surgeons, neurologists, neuroanatomists, neuro-ophthalmologists, neuropathologists, neurophysiologists, psychiatrists, psychologists, roentgenologists and other scientists whose work bears on neurologic surgery. The new constitution stipulated that the number of nonsurgical members shall not be more than one third of the total membership. The highlight of the original group's activities was the celebration in 1939 of the seventieth birthday of Dr. Harvey Cushing. At this time the society presented to him a copy of A Bibliography of the Writings of Harvey Cushing prepared for the occasion. At the time of his death in 1939 Dr. Cushing was emeritus professor at Yale University School of Medicine, New Haven. Officers of the Harvey Cushing Society are Dr. Edgar F. Fincher, Atlanta, Ga., president, Lieut. Comdr. William J. German (MC), U. S. Naval Reserve, vice president, and Dr. Eisenhardt, secretary-treasurer. The society has recognized the importance to neurologic surgery of the related branches such as neurophysiology, neuroroentgenology and neuro-ophthalmology and it is anticipated that these related fields as well as neurologic surgery will find a channel for expression in the new journal.

CANADA

Canadian Medical Association.—The seventy-fifth annual meeting of the Canadian Medical Association will be held in Toronto, May 22-26. In a preliminary announcement the *Canadian Medical Association Journal* states that the association reported the largest membership in its history in 1943, 7,578, including 2,472 in military service, a gain of 608 over the year of 1942 and a gain of 3,577 since the war.

LATIN AMERICA

Health Activities in Latin America.—*Physicians Launch Benefit Program.*—The organization of the "Mexican Mutual Institute of National Medical Progress" has been announced. The movement started with the Confederation of Medical Associations of the Mexican Republic and the Association of Medical Surgeons of the Federal District. Seventy-three drug houses in Mexico City agreed to donate $30,000 to launch the project, promising similar contributions annually. The remainder of the finances necessary are expected to come from the monthly premiums charged members. The program aims to award benefits for old age, invalidism and death as well as to grant assistance to medical colleagues carrying on promising research or who are in need of funds for postgraduate education. The idea stemmed from the "plight of many physicians who, when death, old age or an accident occurs, cannot count on guaranteed protection for themselves and their families." It is pointed out that the support allotted by the private laboratories and drug manufacturers does not in any way carry with it any obligation on physicians to prescribe any particular product. Initially the service will take in twenty-three medical societies in the republic as well as any individual physicians who wish to join. Scholarships will be given for study abroad and support will be offered to research. The institute's capital will be deposited in a bank, and funds will be withdrawn only with the approval of the three sections composing a tripartite directorate representing private practitioners, physicians engaged in group practice and delegates from cooperating laboratories.

Venereal Disease.—The first regional social hygiene conference opened at San Juan the week of January 10 at the School of Tropical Medicine. Dr. Thomas Parran, surgeon general of the U. S. Public Health Service, presented to Dr. Enrique Villela, Mexico City, and Dr. Antonio Fernos-Isern, San Juan, P. R., honorary life memberships in the American Social Hygiene Association. Among the speakers were Dr. Parran; Dr. William F. Snow, New York, chairman of the executive committee of the American Social Hygiene Association; Elliot Ness, director of the Division of Social Protection of the Community War Services, Federal Security Agency; Dr. Charles E. Shepard, director of personnel training and health education, health and sanitation division, Office of the Coordinator of Inter-American Affairs; Sir Ruppert Briarcliff, medical adviser of the comptroller for the development of welfare of the West Indies and medical adviser for Great Britain to the Anglo-American Caribbean Commission; Dr. Donald W. Huggins of the Trinidad Health Service and Major General Morrison C. Stayer, M. C., U. S. Army, surgeon of the Caribbean Defense Command from Panama. February 9 was designated by executive order of Governor R. G. Tugwell as social hygiene day. Another executive order dated February 2 requires the regular venereal disease tests for all insular government employees within thirty days after the beginning of employment. Either a person found to be infected shall be discharged from employment on direction of the commissioner of health or his continued employment shall be conditioned on his compliance with the prescribed course of treatment. Every official and employee of the government shall be examined for syphilis infection by the department of health after the effective date of the executive order, March 1, and shall be reexamined every eighteen months thereafter during the continuance of his employment by the government. The conference and the executive orders constituted the beginning of a concentrated program against venereal disease in Puerto Rico.

Drug Plant Culture Increasing in Central America.—Information from the Office of the Coordinator of Inter-American Affairs indicates an increased development in drug plant culture in Central America. Six quinine plantations are in cultivation in Guatemala. One of these, "El Porvenir," contains about 1,000 acres of cinchona trees and is the largest in the Western Hemisphere (THE JOURNAL, June 12, 1943, p. 457). Cinchona tree nurseries are in operation in Costa Rica under a program in which the Costa Rican government has agreed to make available 10,000 acres for cinchona cultivation. Development of plantation sources of quinine in both countries is carried on with assistance from United States specialists. El Salvador substantially increased production of balsam. Approximately 50,000 trees are capable of an annual yield of from 300,000 to 500,000 pounds of crude balsam. Nicaragua also is increasing balsam production. The report intimated that other medicinal plants in abundance in Central America will be investigated to determine a justification for use.

New Cinchona Project in Costa Rica.—Plans have been made for the planting of about 100,000 cinchona seedlings by the Inter-American Institute of Agricultural Sciences at Turrialba, Costa Rica, to aid in the development of a quinine-producing industry in Latin America, according to Earl N. Bressman, director of the institute, which was established last year as an inter-American agricultural research and development center. The seedlings destined for planting in Costa Rica are part of 2,000,000 cinchona seeds which were taken out of the Philippine Islands in a flying fortress by Col. Arthur F. Fischer just before the fall of Bataan to the Japanese. Colonel Fischer is now liaison officer of the War Department with the United States Office of Foreign Economic Administration, which is cooperating with the other American republics in the expansion of the cinchona industry in the Western Hemisphere to help replace quinine supplies lost in the Far East. The seedlings are of the high-yielding Ledgeriana type, developed in the Far East from cinchona stock originally brought from South America, the home of the cinchona tree. The seeds have been planted temporarily at the United States government plant station at Glendale, Md., from which they are being distributed to Latin America for the expansion of cinchona planting. The arrangements for the planting of 100,000 seedlings at Turrialba, made in cooperation with the War Department and the Foreign Economic Administration, involve the largest single transplanting resulting from the Philippine stock. Previously a trial lot of 1,000 of the seedlings had been sent to Turrialba. It was stated that the first batch of seedlings had done so well in Costa Rica it is logical to undertake a larger scale operation.

FOREIGN

Nuffield Grant for Plastic Surgery Unit.—The Nuffield Provincial Hospitals Trust has given the University of Oxford £8,000 for ten years toward the cost of establishing and maintaining a plastic surgery unit there, *Science* reports. Dr. Thomas Pomfret Kilner has been made the first director of the plastic surgery unit with the title of Nuffield professor of plastic surgery. Hospital facilities will be provided by the Radcliffe Infirmary, to be supplemented by the Ministry of Pensions, according to *Science*.

Foreign Letters

LONDON

(From Our Regular Correspondent)

Jan. 29, 1944.

All Hospitals to Organize Rehabilitation Services

The Ministry of Health has issued a memorandum on rehabilitation to hospitals. It points out that the experience of the last few years has widened the conception of rehabilitation. Instead of being regarded as an ancillary department of a hospital, confined to a limited group of selected patients, it is now becoming recognized as a form of therapy applicable to almost every type of illness or injury, in lesser or greater degree, and affecting the whole period of hospitalization and convalescence. Experience gained during the war in the treatment of psychiatric disorders shows that under expert guidance much can be done by rehabilitation to restore loss of function.

The full realization of the new conception involves: 1. The introduction of rehabilitation into every ward, adapted to individual complaints and stages of recovery, and commencing on the admission of the patient or as soon thereafter as possible. 2. The planning of convalescence with a view to speeding up the recovery of physical and psychologic function and hastening the return to full activity. Until now convalescence, particularly of hospital patients, has been largely haphazard, and valuable time has been lost which could have been saved by careful planning. 3. Appropriate forms of rehabilitation therapy for nearly all types of inpatient disability and for selected groups of outpatients. Patients with sprained joints, septic hands, chest complaints and similar conditions would recover more rapidly and completely if facilities for rehabilitation were available. 4. The provision of expert supervision throughout the whole period of rehabilitation, and the planning of each patient's day to include the right proportion of suitable activities and rest.

The various activities employed at different stages of rehabilitation include (1) passive physical therapy (heat, massage and electrotherapy), (2) remedial exercises, (3) organized games, both indoor and outdoor, (4) occupational therapy undertaken either in bed or in special departments and consisting of either diversional therapy to distract the patient's attention from his illness or remedial therapy adapted to exercising particular groups of muscles, (5) domestic services, such as ward and kitchen work in the hospital, whose value is chiefly psychologic, (6) lectures and debates, (7) social care and (8) industrial guidance. Clearly the days of "lazing" in the hospital are gone. A woman recovering from pleurisy or an abdominal operation, instead of lying in bed with nothing to occupy her mind except worry about the future of her family, will do exercises and handicrafts designed to prevent weakness and keep up her general health.

Extension of the School Medical Service

A new education bill expands the school medical service, which heretofore has been concerned with medical inspection of school children, determining the level of mental and physical development and referring for special examination and treatment children discovered to have mental or physical defects. Except in certain large school authorities, little provision has been made for treatment, which is left to private practitioners and hospitals. The new bill imposes on local authorities the provision of treatment, other than treatment at home, of all children and young persons attending maintained schools and colleges. This treatment is to be free. Moreover, the benefit of medical services is to be extended to schools which are not maintained. The duties of the school medical officer are considerably extended with regard to the handicapped child. Not only is attendance at special schools made compulsory for children at the age of 5 years, instead of at 7 as heretofore, but parents have the right to ask for special examination of any child over the age of 2. Development of the nursery school will also bring more young children under the care of the school medical officer.

The new bill is a further example of the tendency of the state to control more and more the practice of medicine. The passage of the national health insurance act thirty years ago was a great step in this direction. It provided for the medical treatment by general practitioners of all employed persons earning below $1,000 annually. In 1941 this income limit was raised to $1,680. Further extension of the insurance act to the dependents of insured persons was proposed before the revolutionary Beveridge plan was launched. At the lowest estimate this plan provides for the free treatment (apart from insurance payments) of 90 per cent of the population and threatens the extinction of private practice. This probably will not take place at once, but private practice seems likely to diminish as time passes. The whole movement is a manifestation of the socialistic trend in our legislation, which no political party seems willing to oppose. As the changes mentioned show, not even the greatest war in history, involving the most serious peril ever faced by this country, has even temporarily arrested this trend.

Inadequate Food and Medical Supplies in German Prison Camps

At the Royal Society of Medicine two repatriated medical officers, Major J. H. T. Challis and Major G. C. Steele, gave a disturbing account of the food and medical supplies in German prison camps for British soldiers. The food was so poor and scanty, consisting mainly of potato soup, that wounds healed slowly before Red Cross parcels arrived. There was almost complete absence of anesthetics for operations. Complete modern drugs and appliances could not be expected, and there was not even a sufficiency of ether or chloroform or the means for administering them. When the prisoners received the nourishing food in the Red Cross parcels, progress in the healing of their wounds was impressive. The Geneva Convention lays down that the drugs and equipment of hospitals for prisoners must be provided by the belligerent which controls them, but the Germans fail to maintain an adequate standard.

Marriages

Charles H. Cronk, Bloomfield, Iowa, to Mrs. Rosamond Skyhawk of Rochester, Minn., in Lancaster, Mo., December 25.

Arthur G. Baker, Grand Rapids, Mich., to Miss Theresa M. Randolph of Port Huron in Ann Arbor, December 18.

Charles Porter Blunt III, Lynchburg, Va., to Miss Mary Elizabeth Prillaman of Martinsville, December 28.

Edgar Newman Weaver, Orange, Va., to Miss Evelyn Dabney Richards of Roanoke, December 20.

Joseph Shelton Bower, Salem, Va., to Miss Merietta Bagley McGhee of Altavista, December 18.

John H. Sherlock, Rock Rapids, Iowa, to Miss Hilda Bergeson in Morton, Minn., January 1.

James T. Gianoulis, High Point, N. C., to Lieut. Velma Holt at Algiers, Africa, January 31.

Woodrow W. Lovell, Columbus, Miss., to Miss Carolyn Howell of Atlanta, Ga., January 4.

Robert Clark Jones, New York, to Miss Elizabeth Pitcher of Camden, Maine, January 7.

Jay S. Goodman to Miss Fanny Prudowsky, both of Milwaukee, January 21.

Deaths

Harlan Shoemaker ✠ widely known as a leader in the medical profession of southern California, died at St. Vincent's Hospital, Los Angeles, Dec. 11, 1943, following coronary occlusion with a myocardial infarct. Dr. Shoemaker was born at Martelle, Iowa, July 21, 1875. He received his A.B. from Stanford University in 1899 and his M.D. from the University of Pennsylvania Department of Medicine in 1902. Until 1904 he was associated as an intern and resident in surgery with the Methodist Hospital and with the Municipal Hospital in Philadelphia. He practiced in Philadelphia from 1904 to 1910 and then became surgical chief of the Shelby Hospital, Shelby, N. C., from 1910 to 1913. In 1912 he was licensed in California. He later became associated with the Los Angeles County Medical Association and held the position of secretary-treasurer from 1919 to 1930, serving at the same time on the board of trustees. He became president of the Los Angeles County Medical Association in 1936 and served again on its board of trustees from 1939 until the time of his death.

HARLAN SHOEMAKER, M.D., 1875-1943

During the first world war Dr. Shoemaker was surgical examiner for District 17 and took part also in the work of rehabilitation of correctable defects. He was at the time of his death, and had been for years, senior surgeon at the Los Angeles County General Hospital, where in 1937 he was chief of the surgical staff. He had been clinical professor of surgery at the University of Southern California School of Medicine since 1920. He was a fellow of the American College of Surgeons and a member of the College of Physicians of Philadelphia, the Association of Military Surgeons of the United States and the Los Angeles Surgical Society.

Dr. Shoemaker will long be remembered for his leadership in medical affairs in the city of Los Angeles. He first conceived the idea of a permanent headquarters for the Los Angeles County Medical Association. He gave greatly of his time to the raising of money and to the negotiations necessary for the purchase of the property. As a result largely of his efforts the Los Angeles County Medical Association now owns a magnificent building which is its headquarters and also the ground on which the Wilshire Medical Building stands and from which the medical society derives a considerable income. He stimulated the development of the *Bulletin* of the Los Angeles County Medical Association and was largely responsible for the development of an excellent library. Many of the important activities and properties of the Los Angeles County Medical Association stand as a memorial to the devoted efforts of Dr. Harlan Shoemaker.

Sanford Robinson Gifford ✠ Chicago, distinguished ophthalmologist, died in Passavant Memorial Hospital, February 25, aged 52, of virus pneumonia after a short illness.

Dr. Gifford was the son of Dr. Harold Gifford, widely known as an ophthalmologist. He was born in Omaha, Jan. 8, 1892. After graduating at Cornell University, Dr. Gifford received the degree in medicine at the University of Nebraska College of Medicine, Omaha, in 1918. He then served as bacteriologist in the U. S. Army during World War I with the rank of first lieutenant. He returned to Omaha in 1919, where he practiced with his father until 1929. He was instructor in ophthalmology at the University of Nebraska College of Medicine from 1919 to 1924, when he became assistant professor. In 1929 he joined the staff of Northwestern University Medical School, Chicago, as professor and chairman of the department of ophthalmology, a position he held at the time of his death. He was head of the department of ophthalmology, a member of the staff of Passavant and had been attending ophthalmologist at Cook County Hospital since 1932.

SANFORD ROBINSON GIFFORD, M.D., 1892-1944

Dr. Gifford was a member of numerous scientific groups, including the American Ophthalmological Society, American Academy of Ophthalmology and Otolaryngology, Association for Research in Ophthalmology, American College of Surgeons, the Institute of Medicine of Chicago and various honorary medical fraternities. He was certified by the American Board of Ophthalmology and the American Board of Plastic Surgery. In addition to many monographs on the bacteriology of the eyes, especially diseases due to fungi and higher bacteria, Dr. Gifford was the author of A Handbook of Ophthalmic Therapeutics and A Textbook of Ophthalmology. With Dr. J. M. Patton he reported the probable etiologic agent of the hitherto unknown disease, agricultural conjunctivitis. He had been associate editor of the *Archives of Ophthalmology* since 1928, a prolific contributor to the *American Journal of Ophthalmology* from the time he graduated in medicine until 1928 and corresponding editor of the *Klinische Monatsblätter für Augenheilkunde*.

The death of Dr. Gifford brought to an untimely end a brilliant career. He combined the research spirit with an exceedingly practical mind and was thus a leader in ophthalmic research and education as well as in the practice of ophthalmology. He was a cultured physician, with a profound interest in literature, music and the arts. His death leaves many vacancies in the civic, cultural and medical life of Chicago.

Clement Colfax Whitcomb ✠ Colonel, U. S. Army, retired, St. Petersburg, Fla.; Medical School of Maine, Portland, 1891; served as a contract surgeon in the U. S. Army from July 28, 1900 to July 14, 1901; entered the medical corps of the U. S. Army as an assistant surgeon on July 15, 1901; promoted through the various grades to that of colonel on June 29, 1927; retired August 31, 1932 at his own request after thirty years' service; served with the American Expeditionary Forces in France during World War I; from 1919 to 1931 served as finance and supply officer in the surgeon general's office; fellow of the American College of Surgeons; member of the Association of Military Surgeons of the United States; received the award of the Legion of Honor of France and the Medal of Honor of Poland; died in the Veterans Administration Facility, Bay Pines, November 9, aged 75, of obstructive jaundice due to stricture of the common bile duct and chronic adhesive peritonitis.

Walter Lester Carr, Greenfield, Mass.; University of the City of New York Medical Department, New York, 1882; member of the Medical Society of the State of New York and the New York Academy of Medicine; member and past president of the American Pediatric Society; past president of the Medical Society of the County of New York and the American Association of Medical Milk Commissions; specialist certified by the American Board of Pediatrics, Inc.; clinical professor of pediatrics emeritus at the University and Bellevue Hospital Medical College, New York; served as consulting pediatrician at the Letchworth Village, Thiells, N. Y., New York Eye and Ear Infirmary, Woman's Hospital and the City Hospital, New York; formerly director of the department of pediatrics at the Midtown Hospital, New York; editor of "Practice of Pediatrics" published in 1906; collaborator, *Archives of Pediatrics;* died February 2, aged 84, of nephritis and myocarditis.

Samuel Goodwin Gant, Miami, Fla.; Missouri Medical College, St. Louis, 1887; member of the Medical Society of the State of New York and the American Proctologic Society; formerly professor and chief of the department for diseases of the colon, rectum and anus at the Broad Street Hospital Graduate School of Medicine, and professor of diseases of the colon, rectum and anus at the New York Post-Graduate Medical School and Hospital, New York; served as attending coloproctologist to the Broad Street and Harbor hospitals, consultant to the Hospital for Joint Diseases, New York, Huntington (N. Y.) Hospital, Jewish Memorial Hospital, New York, and Hackensack (N. J.) Hospital, and to Sing Sing Prison; author of "Constipation, Obstipation and Intestinal Stasis" and "Diseases of the Rectum, Anus and Colon"; died in the Victoria Hospital January 22, aged 69, of pneumonia.

William Pearce Coues ✠ Brookline, Mass.; Harvard Medical School, Boston, 1894; served as instructor in clinical surgery at the Tufts College Medical School, Boston, and assistant in surgery at his alma mater; member of the New England Dermatological Society; fellow of the American College of Surgeons; a captain in the medical corps of the U. S. Army during World War I; for many years secretary of the Massachusetts Society of Examining Physicians; examiner for the Massachusetts Industrial Accident Board for twenty-five years; formerly examining physician for Boston schools; served on the staffs of the Massachusetts General Hospital and Boston Dispensary; consulting surgeon, the Massachusetts Eye and Ear Infirmary, Boston; trustee of the Brookline Historical Society; died January 13, aged 71, of angina pectoris and myxedema.

William Forester Davison, Kingston, Pa.; Jefferson Medical College of Philadelphia, 1896; member of the Medical Society of the State of Pennsylvania; during World War I a member of the local examining board for division number 4, Luzerne County, and later commissioned a first lieutenant in the medical corps of the U. S. Army, transferred to Camp Lee as head of the intelligence department at the base hospital; chairman of the Pennsylvania Association of Dairy and Milk Inspectors; served as supervising medical inspector of the schools in Luzerne and Lackawanna counties; medical director of Luzerne County; on the staff of the Nesbitt Memorial Hospital; died January 9, aged 76, of coronary embolism.

Henry Herrington Asher, Manistique, Mich.; University of Kansas School of Medicine, Kansas City, Kan., 1934; member of the Kansas Medical Society; health officer of Alger and Schoolcraft counties; formerly director of the division of local health of the Kansas State Board of Health; for two years health officer of Sedgwick County, Kan.; at one time health officer of district number 6 in Missouri, consisting of fourteen counties; captain, medical reserve corps, U. S. Army, not on active duty; died in the Munising Hospital, Munising, January 13, aged 34, of pneumonia.

Harry Holyroyd Ainsworth, Birchwood, Wis.; College of Physicians and Surgeons of Chicago, 1895; member of the State Medical Society of Wisconsin; past president of the Barron-Washburn-Sawyer-Burnett Counties Medical Society; formerly served as a member and president of the state board of health; served during World War I; on the staff of the Northern Wisconsin Colony and Training School, Chippewa Falls; died January 8, aged 71, of cardiac decompensation.

Mira May Allen, Rochester, N. Y.; University of Michigan Department of Medicine and Surgery, Ann Arbor, 1899; for many years associated with the Rochester Health Bureau; served as assistant director of the child hygiene division, Indiana State Board of Health, Indianapolis; formerly in charge of a colony of 1,000 French children at Dinard, France; died January 10, aged 73, of pneumococcic meningitis and osteoarthritis.

Frank R. Atkins, Caruthersville, Mo.; Missouri Medical College, St. Louis, 1883; at one time physician and surgeon for the Hollady Klotz Land and Lumber Company, Greenville; died January 5, aged 84, of senility.

Joseph B. Bailey ✠ Clyde, Texas; Memphis (Tenn.) Hospital Medical College, 1903; on the staff of the Hendrick Memorial Hospital, Abilene, where he died January 3, aged 65, of coronary thrombosis.

Ephraim S. Barger, Omaha, Ill.; Marion-Sims College of Medicine, St. Louis, 1899; also a druggist; died in the Ferrell Hospital, Eldorado, January 1, aged 81, of nephritis.

Frank Talmage Barker ✠ Tampa, Fla.; University of Maryland School of Medicine and College of Physicians and Surgeons, Baltimore, 1919; U. S. Naval Medical School, 1922; formerly secretary of the Hillsborough County Medical Society; at one time served in the medical corps of the U. S. Navy; on the staffs of the Tampa Municipal and St. Joseph's hospitals; died suddenly January 5, aged 47, of coronary thrombosis.

Alexander Chambers Blair, Pittsburgh; Hahnemann Medical College and Hospital of Philadelphia, 1898; member of the Medical Society of the State of Pennsylvania; on the staffs of the Homeopathic Medical and Surgical Hospital, now the Shadyside Hospital, and the Allegheny General Hospital; died January 4, aged 74, of arteriosclerosis.

Fred Eugene Butler Jr. ✠ Salem, Mo.; University of Kansas School of Medicine, Kansas City, 1930; secretary-treasurer of the Dent County Medical Society; a first lieutenant in the medical reserve corps of the U. S. Army not on active duty; served on the staffs of the Evangelical Deaconess Home and Hospital, St. Louis, Nelle McFarland Memorial Hospital, Rolla, and the Trinity Lutheran Hospital, Kansas City; died in the Missouri Baptist Hospital, St. Louis, January 3, aged 40, of myocarditis.

Matthew Thompson Dingess ✠ Atchison, Kan.; Kentucky School of Medicine, Louisville, 1890; surgeon for the Burlington and Santa Fe Railways; on the staff of the Atchison Hospital, where he died January 8, aged 76, of pneumonia.

Edwin J. Dorminy, Fitzgerald, Ga.; University of Maryland School of Medicine, Baltimore, 1890; member of the Medical Association of Georgia; formerly a member of the state house of representatives and senator; served as a councilman, county physician, and director in the local banks; president of the Fitzgerald Hospital; died January 13, aged 76, following a laminectomy.

William Milas Dunn ✠ Atlanta, Ga.; Johns Hopkins University School of Medicine, Baltimore, 1911; lieutenant in the U. S. Navy during World War I; on the staffs of the Crawford W. Long Memorial, Piedmont, Emory University and Grady hospitals and St. Joseph Infirmary; died in the Veterans Administration Facility, January 4, aged 62, of cerebral hemorrhage.

Richard Gardner Eaton, Sedro Woolley, Wash.; Harvard Medical School, Boston, 1896; member of the American Psychiatric Association; served in the medical corps of the U. S. Army during World War I; at one time superintendent of the Idaho Insane Asylum, Blackfoot; for many years served on the staffs of various Veteran Administration facilities; on the staff of the Northern State Hospital, where he died January 7, aged 74, of influenza and pneumonia.

Simon Ehrlich, Boston; Middlesex College of Medicine and Surgery, Cambridge, Mass., 1926; on the staffs of the Harley Private Hospital and the Forest Hills General Hospital, Forest Hills; died in the Allerton Hospital, Brookline, Mass., January 4, aged 46, of coronary thrombosis.

Leslie Carlisle Fisher, Green Cove Springs, Fla.; Atlanta (Ga.) School of Medicine, 1909; served on the city commission and at one time as mayor of Green Cove Springs; member of the Rotary Club; died January 8, aged 59, of heart disease.

Luke Joseph Fleming, Tarrytown, N. Y.; Bellevue Hospital Medical College, New York, 1893; attending physician at the Tarrytown Hospital, where he died January 23, aged 75, of uremia, nephrosclerosis and hypertensive cardiovascular disease.

Walter S. Given, Indianapolis; Central College of Physicians and Surgeons, Indianapolis, 1901; at one time assistant professor of gastrointestinal surgery at the Indiana University School of Medicine; served during World War I; died in the Veterans Administration Facility, Hines, Ill., January 22, aged 65, of carcinoma of the esophagus.

D. H. Godsey, Hartford, Ky.; Hospital College of Medicine, Louisville, 1901; a member of the local draft board number 130; died January 6, aged 73, of angina pectoris.

Gould Shelton Higgins, South Coventry, Conn.; Yale University School of Medicine, New Haven, 1901; died in the Windham Community Memorial Hospital, Willimantic, January 5, aged 68, of an accidental overdose of pentobarbital sodium.

James Hinchliff, Minburn, Iowa; Keokuk Medical College, College of Physicians and Surgeons, 1905; member of the board of education and town council; died January 10, aged 64, of hypostatic pneumonia and cerebral hemorrhage.

George McClintoc Hutchison ✠ Ridgway, Pa.; Medico-Chirurgical College of Philadelphia, 1907; formerly a dentist; fellow of the American College of Physicians; on the staff of the Andrew Kaul Memorial Hospital, St. Marys; died in the Cleveland Clinic Foundation Hospital January 6, aged 68, of peritonitis.

Jesus Daniel Ibarra, San Antonio, Texas; Universidad Nacional Facultad de Medicina, Mexico, D. F., 1902; died in the Santa Rosa Hospital January 7, aged 63, of lobar pneumonia.

Jeremiah Swain Irwin ✠ Erie, Pa.; Medico-Chirurgical College of Philadelphia, 1906; served on the staffs of St. Vincent's and Hamot hospitals; found dead in his car January 18, aged 62, of coronary thrombosis.

John Francis Xavier Jones, Philadelphia; University of Pennsylvania Department of Medicine, Philadelphia, 1907; Jefferson Medical College of Philadelphia, 1910; fellow of the American College of Surgeons; served in the U. S. Navy during World War I; on the staffs of the Jefferson, Misericordia, St. Agnes and St. Joseph's hospitals; died in the Veterans Administration Facility, Coatesville, January 7, aged 63, of pneumonia.

Julius Calvin Oram ✠ South Portland, Maine; Bowdoin Medical School, Portland, 1915; president of the Cumberland County Medical Society; served in the medical corps of the U. S. Army during World War I; for two terms served on the school committee; at one time city physician; member of the staffs of the Maine General Hospital, Maine Eye and Ear Infirmary, and Portland City Dispensary; a director of the South Portland Building and Loan Association; died in the Deaconess Hospital, Boston, November 19, aged 58, of status asthmaticus.

Finley Van Orsdall, Baton Rouge, La.; Medical College of Ohio, Cincinnati, 1902; served as an acting assistant surgeon in the U. S. Public Health Service; for many years chief of bureau of communicable diseases, Ohio State Department of Health at Columbus; at one time on the staff of the Murphy Sanatorium, Albuquerque, N. M.; died January 11, aged 69, of cerebral hemorrhage.

Robert Eugene Pugh, Lawton, Okla.; University of Oklahoma School of Medicine, Oklahoma City, 1936; member of the Oklahoma State Medical Association; on the staff of the Angus Hospital; died at Haskell in November, aged 32, of nephritis and hypertension.

Thomas Minor Redd, Atlantic City, N. J.; Jefferson Medical College of Philadelphia, 1887; died in the Atlantic City Hospital December 31, aged 79, of bronchopneumonia, nephritis, myocarditis and arteriosclerosis.

Henry Jesse Spalding ✠ Union City, N. J.; Cornell University Medical College, New York, 1900; physician for the Selective Service during World War I and World War II; consulting physician at the North Hudson Hospital, Weehawken, and the Christ Hospital, Jersey City; died December 27, aged 67, of coronary thrombosis and arteriosclerotic heart disease.

Frederick William Steiner ✠ Havre de Grace, Md.; College of Physicians and Surgeons, Baltimore, 1907; past president of the Harford County Medical Society; chief of staff of the Harford Memorial Hospital; second vice president, Havre de Grace Banking and Trust Company and president of the City Building and Loan Company; died in the Union Memorial Hospital, Baltimore, November 25, aged 65, of injuries received in an automobile accident.

Samuel Topkins, Brooklyn; University of Vermont College of Medicine, Burlington, 1915; on the staff of the Israel Zion Hospital, where he died December 28, aged 57, of coronary sclerosis.

Samuel William Treptow, San Diego, Calif.; Memphis (Tenn.) Hospital Medical College, 1891; died December 24, aged 76, of cerebral hemorrhage.

Ethon L. Trevitt, West Point, Iowa; Eclectic Medical Institute, Cincinnati, 1887; died in Fort Madison December 7, aged 81, of pernicious anemia.

William Frederick Turner, Cranford, N. J.; University of Pennsylvania Department of Medicine, Philadelphia, 1879; died December 30, aged 87, of influenza and arteriosclerosis.

Sylvester Ulrich, Elizabethtown, Pa.; Hahnemann Medical College and Hospital of Philadelphia, 1890; member of the Medical Society of the State of Pennsylvania; on the staff of St. Joseph's Hospital, Lancaster, where he died January 4, aged 81, of cerebral hemorrhage.

William Henry Vail, Newark, N. J.; College of Physicians and Surgeons of Columbia College, New York, 1869; oldest alumnus of Princeton University, the Columbia University College of Physicians and Surgeons, New York, and the Blair Academy, Blairstown; a trustee of the academy for many years; died December 31, aged 98, of chronic myocarditis.

Archibald Walter Ward, Minneapolis; University of Nebraska College of Medicine, Omaha, 1911; member of the Minnesota State Medical Association; fellow of the American College of Surgeons; on the staffs of the Asbury Hospital and the Swedish Hospital, where he died recently, aged 61, of cerebral hemorrhage, hypertension and orbital abscess.

John Piper Williams ✠ Lincoln, Neb.; Northwestern University Medical School, Chicago, 1896; served during World War I; life member of the chamber of commerce; on the staff of St. Elizabeth Hospital; died December 13, aged 70, of carcinoma of the liver.

Benjamin Ezra Wood ✠ Canton, Mass.; Harvard Medical School, Boston, 1906; resident member of staff, Massachusetts Hospital School; died December 25, aged 64, of cerebral hemorrhage.

Joseph Bidmead Wright, Pasadena, Calif.; University of the City of New York Medical Department, New York, 1879; formerly on the staffs of the New York Polyclinic Medical School, New York, and North Eastern Dispensary, New York; died January 8, aged 85, of coronary arteriosclerosis.

Kate E. Geiger Yont, Denver; University of Michigan Department of Medicine and Surgery, Ann Arbor, 1896; member of the Colorado State Medical Society; died in the Mercy Hospital December 7, aged 71, of carcinoma of the rectum and sigmoid.

Edgar Nelson Young, San Diego, Calif.; College of Physicians and Surgeons, Los Angeles, 1912; member of the California Medical Association; died in the Mercy Hospital December 23, aged 58, of cerebral embolus and mitral stenosis.

DIED WHILE IN MILITARY SERVICE

Porter Madeira Hoidale ✠ Surgeon, Lieutenant Commander, U. S. Navy, Tracy, Minn.; University of Minnesota Medical School, Minneapolis, 1940; received his B.A. from Carleton College, Northfield, Minn., in 1931; he then entered the aviation branch in the Marine Corps, taking his training at Great Lakes, Pensacola, Fla., and Coronado Air Base, San Diego; commissioned lieutenant Aug. 4, 1939; began extended active duty in the U. S. Marine Corps as a captain (naval aviator) Nov. 25, 1940; while at San Diego he requested transfer from the Marines to the Navy, which was granted by special act of congress to secure his full rank status; entered the medical corps of the U. S. Navy as a passed assistant surgeon, lieutenant on March 20, 1942; ordered to active duty in the New Hebrides area Aug. 8, 1942 as flight surgeon on the staff of Admiral Fitch, where he served for six months; later transferred to the aircraft carrier *Enterprise;* chief medical officer of the naval air base at Klamath Falls, Ore., died in a hospital at Klamath Falls, January 23, aged 34, of a head injury received January 12.

Bureau of Investigation

STIPULATIONS

Agreements Between Federal Trade Commission and Promoters of Various Products

Following are abstracts of stipulations in which promoters of "patent medicines," medical devices and cosmetics have agreed, following action by the Federal Trade Commission, to discontinue certain misrepresentations in their advertising. These stipulations differ from the "Cease and Desist Orders" of the Commission in that such orders definitely direct the discontinuance of misrepresentations. The abstracts that follow are presented primarily to illustrate the effects of the provisions of the Wheeler-Lea Amendment to the Federal Trade Commission Act on the promotion of such products:

Blackstone Hair Coloring.—The Federal Trade Commission reported this to be a coal-tar hair dye, and objected to some of the advertising claims for it, such as that it restores hair to its natural color and is harmless to use, whereas it contains ingredients which may cause skin irritation to certain individuals. In April 1943, the promoter, W. T. Boomer, trading as Boomer's Mail Order Service, Portsmouth, Va., entered into a stipulation with the Federal Trade Commission, agreeing to discontinue any advertisement which failed to state that this product contains ingredients which may cause skin irritation to certain users and hence a preliminary test according to accompanying directions should first be made, besides the accompanying caution that the product should not be used for dyeing the eyelashes or eyebrows, lest it cause blindness. The stipulation provided, however, that if the label should bear these warnings conspicuously, it would be sufficient for the advertisement to contain only the statement, "Caution: Use only as directed on the label."

Chartered University of America.—This was a Huron, S. D., corporation, with W. A. Johns, Julia W. Johns and Isaiah O. Hagen as directors. They were charged by the Federal Trade Commission with false advertising and misrepresentation in connection with the sale to purchasers in India of so-called diplomas purporting to evidence the conferring of scholastic degrees. In March 1943 they stipulated with the Commission that they would desist from false advertising and from using the words "university," "medical council" or "board of examinations" in their corporate or other trade name, or any other word of like meaning in any manner which might give the impression that they conduct such institutions. Further, they agreed to cease representing, through the issuance of so-called diplomas or degrees which purport to have been conferred by a fully qualified educational institution, that their business is that of a university or an institution of learning. In addition, they were no longer to represent that they issue diplomas or degrees that are recognized or accepted by any reputable college or university, or that these incorporators themselves have had such degrees as M.A., LL.D. or Ph.D., which they have used after their names, conferred on them by an accredited college or institution.

Formula 234, Skin Peel.—This was the subject of an agreement between Winslow Chase, trading as the Thaxly Company, Washington, D. C., and the Federal Trade Commission. In this Chase stipulated that he would cease representing that his product is harmless and discontinue any advertising which failed to reveal that the preparation should not be administered except under the direct and continual supervision of a physician. Further, Chase agreed to drop from his advertising certain claims as to the effectiveness or quality of products made from formulas that he sold for hair tonics and other cosmetics.

Hollywood Liquefier.—This was put out by one Seremus Wills, trading as Hollywood Liquefier Sales, Los Angeles, and was intended for pulverizing and reducing fruits and vegetables to a puree or a semi-liquid condition. In February 1943 Wills entered into a stipulation with the Federal Trade Commission, agreeing to discontinue certain advertising representations, such as that, among other things, fruits or vegetables must be reduced to a semi-liquid state in order to be digested; that his device renders the nutritive substances in fruits, vegetables, meats or nuts more easily digestible than in their customary forms; that the ordinary diet is deficient in vital organic materials found in fresh fruits or vegetables, or that the cells of fruits or vegetables must be broken down by a mechanical device such as the one he sells.

Lak and Lak Plus.—These are sold by a Los Angeles concern calling itself Makers of Kal, Inc., which in March 1943 stipulated with the Federal Trade Commission that it would cease misrepresenting the therapeutic properties of these products, as follows: That they improve bowel health, exercise intestinal muscles or constitute a remedy or cure for constipation or a treatment for sluggish digestion or for any condition of nervousness, or eliminate poisonous waste from the body, build resistance to fatigue or improve the general state of health.

Milkmaid Cosmetics.—These are put out by Milkmaid, Inc., New York, and Lorr Laboratories, Paterson, N. J. In April 1943 these concerns and the H. M. Kiesewetter Advertising Agency, Inc., New York, stipulated with the Commission that they would cease representing that the preparations will nourish the skin or that the cosmetic designated "Milkmaid Emulsion" contains milk or cream. Further, in advertising this particular product, they agreed to discontinue using the word "Milkmaid" unless in direct conjunction therewith it is stated that the preparation does not contain milk.

Min-O-Ral.—That this mineralized water, when taken as directed, would be of any therapeutic value other than in the treatment of iron deficiencies or, when administered externally, would offer any benefit other than that of an inhibitory antiseptic or an astringent or styptic were advertising misrepresentations which Steve Ladas and Olga Spanpapolos, trading as the Min-O-Ral Products Company, Detroit, agreed to discontinue in a stipulation which they entered into with the Federal Trade Commission in March 1943. Further, they agreed to cease representing that the product provides an adequate treatment or permanent or temporary relief for headaches, kidney or bladder disorders, arthritis, gout, or stiffening of the joints, or that it will overcome fatigue, provide energy, correct weakness or underweight, or promote resistance to infections or run-down conditions resulting from impoverished blood, improper elimination or any other cause.

Nu-Yorkers' Infra-Red Scalp Cap and Nu-Yorkers' Infra-Red Beauty Mask.—A. O. Dyke, Miami, Fla., trading as The Nu Yorker, stipulated with the Federal Trade Commission in March 1943 that in the sale of these devices he would cease making the following misrepresentations in his advertising: That either the Cap or the Mask constitutes an adequate treatment or dependable relief for sinus congestion or head colds, has any alkaline or antiseptic effect, is of value in treating nervous diseases, destroys germ life or has any effect on the action of the skin other than as a temporary stimulant of the flow of blood or perspiration. He further agreed to cease using the word "Infra-Red" or other words of like meaning which might give the impression that any material heating effect resulting from use of these devices is produced by infra-red radiation; and such phrases as "low, medium and high heat," which might imply that the devices are capable of maintaining three different, distinct degrees of heat.

Regina.—This coal-tar hair dye is put out by Humbert Cagnazzi, Gaetano Visceglie and Nelson Torelli, trading as the Nem Company, New York. In March 1943 these persons entered into a stipulation with the Federal Trade Commission to cease making the advertising misrepresentation that their dye contains an ingredient which will provide the user with special or unique benefits, and to discontinue any promotion which fails to warn the user of Regina that the product contains ingredients which may cause skin irritation to certain individuals, requires a preliminary test, and should not be used for dyeing the eyelashes or eyebrows, lest it cause blindness. The stipulation provided, however, that the advertisements need contain only the statement, "Caution: Use only as directed on label" if the said labeling should bear the proper warning and adequate directions for the preliminary test.

Tissue Food Tablets A and B, Cerate, and Head-Hold Spine-Stretch Harness.—These are put out by Florence English Henry, trading as Dr. V. P. English, San Diego, Calif. In March 1943 she stipulated with the Federal Trade Commission that she would discontinue the following misrepresentations, among others, in connection with her advertising: That the medicines and the body harness, used alone or in combination, as directed or otherwise, constitute a remedy, cure, or an aid in the treatment of displaced vertebrae or spinal irritations, nerve pressure, spinal pains, hysteria, insanity and certain ailments of the stomach, liver and kidneys, as well as rheumatism, paralysis, sciatica and eye diseases; that her Cerate is a superior remedy or cure for burns, cuts or chapped skin or has any value other than as a mild counterirritant; that the body harness pulls vertebrae in the spine away from each other, stops the "squeeze" on spinal nerves between the bones, or relieves pain and distress caused by pressure on the nerves, and that her "Book No. 4" shows how to relieve spinal irritation or that by its method relief can be given by another person. Florence Henry further agreed to discontinue using the words "Tissue Food" in the brand name of her other preparations, or otherwise representing that they constitute a food for tissues.

Vitalix Reducing Plan.—This "treatment" was promoted by Vitalix, Inc., Canton, S. D., and consisted of "Mild Laxative Tablets" and "Active Laxative Tablets," supplemented by a "Reducing Week Diet" and a "Normal Week Diet," with a list of exercises added. In March 1943 the concern entered into a stipulation with the Federal Trade Commission, agreeing not to publish any advertisement which would fail to reveal that its "Reducing Week Diet" may be harmless unless supervised by a physician, or any which did not reveal that the two types of laxative tablets should not be taken in the presence of symptoms of appendicitis, and that the frequent or continued use of them may result in dependence on laxatives. The concern, however, was permitted to limit its warning to the statement, "Caution: Use only as directed" if and when the label contained a warning to the same effect. The company further agreed to cease representing, through the use of the word "Normal" in referring to its "Normal Week Diet," that such a diet allows for normal food consumption.

Vita-Pneumatic Action Truss.—This is sold by one Julius Portnow, trading as the Pneumatic Institute Company, New York. In March 1943 he stipulated with the Federal Trade Commission that he would cease representing that his device is a new discovery or that the use of it will prevent difficulties associated with hernia, or do more than give relief from certain types of this disorder. By the terms of the stipulation Portnow was no longer to represent that he had been a rupture specialist for 42 years or any designated period of time in excess of what is actually the fact, and that the device which he sells is not a truss or that by its use a person would receive medical or non-mechanical treatment that would enable him to dispense with wearing a truss. Portnow also was to cease employing the word "institute" in his trade name or in any manner giving the impression that his business is that of an association engaged in promoting medical science or the art of healing.

Correspondence

HYPERTENSION IN MILITARY SERVICE

To the Editor:—Your editorial in THE JOURNAL, Nov. 13, 1943, page 703, concerning hypertension in military service again raises a question which must be continually plaguing the conscientious medical examiner for the military services and which is beginning to become of considerable practical importance to the civilian physician as more and more young men are rejected for induction or are discharged from the armed services because of borderline or actual hypertensive disease. I am seeing an average of two or three young men each week who have become anxious over the present significance and possible future serious consequences of the finding of an elevated blood pressure by selective service or army or navy medical examiners. Most of these men feel that they would not have been rejected or discharged from the armed services if they had not had a serious degree of hypertensive disease. Actually, the majority of such young men whom I have seen would be classed more reasonably as "vascular hyperreactors," and the question of when or whether they will have serious hypertensive disease is left unanswered.

I agree that the solution of the problem of what to do with persons with a hyperreactive blood pressure cannot be settled practically by rejecting all persons who have an elevated blood pressure on any one reading. Such a procedure would certainly exclude from military service a large group of young men who probably would make efficient or even superior soldiers if some care was taken to see that they were placed in the right kind of job. It is probable that a rather large number of men who are being rejected for this reason might not have significant or disabling hypertensive disease for many years. There seems to be no standard procedure for acceptance or rejection of such men, and indeed it is impossible that such a standard could be set up at the present time with any reasonable degree of reliability. The plain truth is that one does not have sufficient information to answer the question of what to do with the person with transient elevations of blood pressure. Such information was not available at the time of the Civil War or at the time of World War I or at the beginning of World War II, and if one is to be realistic it must be realized that unless this fact is recognized and something is done about it such information will not be available at the time of the next war.

A conclusive answer to the question of what is the significance of varying degrees of hyperreactivity of the blood pressure at different ages in wartime cannot be obtained except by a long distance follow-up study of an adequately large and well controlled group of young men and women who have had especially controlled and recorded preliminary studies of their blood pressure and who have been followed through a war in varying kinds of duties and for from ten to twenty years afterward. The information obtained from studies of special groups such as insurance applicants or army officers or hospital patients or comparative studies of groups of different ages in regard to blood pressure readings and blood pressure reactions to various pressor tests can never do more than indicate the possibilities and emphasize the importance of following a large group of especially controlled individuals through a lifetime in order to obtain conclusive information.

One does not at the present time know with any reasonable certainty the incidence of hypertensive disease at different ages in the general population, the incidence of vascular hyperreactivity or whether it increases with age, or the significance of vascular hyperreactivity as measured by the reaction of the blood pressure to various pressor stimuli. Until one knows the answer to these questions it is not possible to give a conclusive answer to what should be done with the person with transient elevations of blood pressure. One might as well admit that the answer to these questions probably will not be available during this war unless it lasts for ten to twenty years, as some people are predicting, but one should not let the opportunity of eventually obtaining the answer to these questions slip by. One should be gathering and cataloguing information during this war and should have a setup for following it up for many years after the war. It is hoped that such an opportunity will not soon be presented again. It was proposed as long as three years ago that a large enough group of men in the armed services be especially studied with regard to their blood pressure regulating mechanism and that they be followed through their active service and after the war for ten to twenty years by a permanent committee such as the Soldier's Heart Committee of the last war. This is the only way that I can see to obtain an answer to the most pertinent question of the significance of vascular hyperreactivity. My purpose in this letter is to emphasize again the desirability of such a study. I have learned through a personal communication from Dr. Paul D. White, chairman of the Subcommittee on Cardiovascular Diseases of the National Research Council, that certain studies of blood pressure have been under way for the last year or two under the National Research Council and that others are contemplated but, as far as I know, no such study as proposed in this communication has yet been started and the opportunity for making such a study is rapidly being lost unless the war lasts much longer than most people predict.

EDGAR A. HINES JR., M.D., Rochester, Minn.

"YAWS, LEISHMANIASIS AND PINTA"

To the Editor:—Dr. Howard Fox's article on "Yaws, Cutaneous Leishmaniasis and Pinta" (THE JOURNAL, Oct. 23, 1943) contained a few statements which I do not think should go unchallenged, especially as it was stated in a footnote that he will be writing on this subject in a book to be published shortly.

1. The macular eruption mentioned as nearly always absent in yaws is the earliest of the second stage lesions to appear in a typical case of yaws. It appears on the average three to four weeks after the primary lesion and not infrequently.

2. The statement ". . . in the early stages the disease may be permanently cured by three successive injections of neoarsphenamine, though much more treatment is required in the late stage" is misleading. Cure is not effected in a percentage of early cases treated with four to six injections of either neoarsphenamine or bismuth salicylate. I have had several cases with first and early second stage lesions which even gave negative serologic reactions following treatment and yet relapsing lesions developed many months after. Two cases with dark field positive primary lesions of one month's duration, and with no second stage lesions, were treated with six injections of bismuth salicylate. The lesions healed in the usual average length of time, but at six months and at twenty months in the 1 case, and at eighteen months in the other, second stage lesions developed. In addition, it seems inaccurate to use the word "cured" after such limited treatment. In 411 cases of yaws with Wassermann reaction positive treated with six injections of neoarsphenamine the lesions cleared in the usual time but the Wassermann reaction was still positive at the end of six months in 74.56 per cent of these cases; it was positive at the end of one year in 55.03 per cent, at the end of eighteen months in 45.50 per cent and at the end of two years in 31.63 per cent of the cases.

3. With the introduction of specific treatment in several active lesions of gangosa there was apparently no further loss of cartilaginous tissue; therefore to say that this lesion is practically incurable seems unduly pessimistic.

4. The statement "there is eventually complete cross immunity between syphilis and yaws, though there are differences in the immune state in the two diseases" is debatable. It is probable that infection with yaws provides a defense mechanism that

gives some measure of protection against syphilis after some time has elapsed. This protection is even then not necessarily complete. H. M. Hanchell (*Brit. J. Ven. Dis.* **4**:64, 1928) mentions a case in which syphilis was contracted nine years after an attack of yaws and while the Wassermann reaction was still strongly positive as a result of a previous infection with yaws. One of my patients was a woman aged 29 who had been brought up in a yaws endemic area. She was infected with yaws as a child of 9 (the scar of the primary lesion was still on her leg). She had received no treatment. Some years after puberty (eight or nine years later) she had intercourse with several men who had lived in the seaport town of Kingston, Jamaica. When she was 19 years old she gave birth to a daughter. This child was seen at 10 years of age and examined. The facies was typically syphilitic, with frontal bossing, Hutchinson's teeth (with characteristic convergence of the lateral surfaces of the central upper and lower incisors) and saddle nose deformity. The child had also corneal opacity and was blind in the right eye. The mother herself had suffered from a macular rash scattered over her body shortly after beginning her promiscuous life. This case was not reported in my book on yaws, much of the material for which was gained when I was attached to the Yaws Commission, under the Rockefeller Foundation and the government of Jamaica.

H. D. CHAMBERS, M.D.,
Kingston, Jamaica, B. W. I.

CREEPING ERUPTION

To the Editor:—In the issue of THE JOURNAL of Dec. 11, 1943, in a communication to the editor, Lieut. Harvey Blank, M. C., of this hospital reported a case of creeping eruption treated with sodium antimony biscatechol (fuadin) intramuscularly without any apparent benefit. Herewith is a report of a case apparently cured by this method of treatment.

On Dec. 16, 1943 a soldier was admitted to our service with an eruption of the abdomen, chest, right thigh and right upper extremity of two months' duration. A diagnosis of creeping eruption was made. At admission 32 distinct active tracks were seen, and under observation all tracks were noted to be active. Some of the larvae moved as much as ½ to ¾ inch in forty-eight hours. The treatment was as follows:

On December 20, fuadin 1.5 cc. was administered intramuscularly as a test to determine any idiosyncrasy to the drug. Doses of 5 cc. were given on December 21, 22, 23, 24, 25 and 26.

A rest period of one week was allowed the patient, and the injections were continued. Since the patient presented no untoward symptoms and daily urinalyses were negative, it was decided to increase the daily dose to 7 cc., which was given on Jan. 2, 3, 4, 5 and 6, 1944. On the 4th the pruritus of the lesions had greatly diminished. On the 5th there was very little pruritus. The tracks on the abdomen were beginning to fade. On the 6th only seven tracks were active. There remained very little pruritus. On the 8th there were only two active tracks, with practically no pruritus. On the 12th there was only one active lesion, on the dorsum of the right hand. On the 14th there were no active lesions, but the lesion on the hand was slightly pruritic. On the 16th the lesion on the hand was not active, but a small elevated pruritic nodule on the dorsum of the right hand was remaining. On the 22d there were no active lesions, but because the patient was being discharged the pruritic nodule at the end of the track on the dorsum of the hand was sprayed with ethyl chloride. On the 24th the pruritic nodule of the hand was still present. It was sprayed with ethyl chloride. On January 28 the patient was discharged with no active or pruritic lesions.

This, then, is the second reported case of creeping eruption which was benefited by intramuscular injections of sodium antimony biscatechol (fuadin).

SIMON S. RUBIN, Captain, M. C., A. U. S.
Chief of Dermatology and Allergy Section, Headquarters Station Hospital, Camp Livingston, Louisiana.

Medical Examinations and Licensure

COMING EXAMINATIONS AND MEETINGS

NATIONAL BOARD OF MEDICAL EXAMINERS EXAMINING BOARDS IN SPECIALTIES

Examinations of the National Board of Medical Examiners and Examining Boards in Specialties were published in THE JOURNAL, Feb. 26, page 596.

BOARDS OF MEDICAL EXAMINERS

ALABAMA: Montgomery, Oct. 24-26. Sec., Dr. B. F. Austin, 519 Dexter Ave., Montgomery.
ALASKA: Juneau, March 7. Sec., Dr. W. M. Whitehead, Box 561, Juneau.
ARIZONA:* Phoenix, April 4-5. Sec., Dr. J. H. Patterson, 826 Security Bldg., Phoenix.
ARKANSAS:* March. Sec., Dr. D. L. Owens, Harrison. *Eclectic.* Little Rock, June 8. Sec., Dr. C. H. Young, 1415 Main St., Little Rock.
CALIFORNIA: San Francisco, June 27-29 Sec., Dr. Frederick N. Scatena, 1020 N St., Sacramento.
COLORADO:* Denver, April 4-7. Sec., Dr. J. B. Davis, 831 Republic Bldg., Denver.
CONNECTICUT:* *Medical. Written.* Hartford, March 14-15. *Endorsement.* New Haven, March 28. Sec. to the Board, Dr. Creighton Barker, 258 Church St., New Haven. *Homeopathic.* Derby, March 13-14. Sec., Dr. J. H. Evans, 1488 Chapel St., New Haven.
DISTRICT OF COLUMBIA:* *Reciprocity.* Washington, March. Sec., Commission on Licensure, Dr. G. C. Ruhland, 6150 E. Municipal Bldg., Washington.
FLORIDA:* Jacksonville, June 26-27. Sec., Dr. W. M. Rowlett, Box 786, Tampa.
ILLINOIS: Chicago, April 4-6. Supt. of Registration, Department of Registration and Education, Mr. Philip Harman, Springfield.
INDIANA: Indianapolis, May 2-4. Sec., Board of Medical Registration and Examination, Dr. W. C. Moore, 301 State House, Indianapolis.
MAINE: Portland, March 14-15. Sec., Board of Registration of Medicine, Dr. A. P. Leighton, 192 State St., Portland.
MASSACHUSETTS: Boston, March 14-17. Sec., Board of Registration in Medicine, Dr. H. Q. Gallupe, 413-F State House, Boston.
MINNESOTA:* Minneapolis, April 18-20. Sec., Dr. J. F. DuBois, 230 Lowry Medical Arts Bldg., St. Paul.
MISSOURI: St. Louis, August. Sec., State Board of Health, Dr. James Stewart, State Capitol Bldg., Jefferson City.
MONTANA: Helena, April 3-5. Sec., Dr. O. G. Klein, First National Bank Bldg., Helena.
NEW HAMPSHIRE: Concord, March 9-10. Sec., Board of Registration in Medicine, Dr. D. G. Smith, State House, Concord.
NEW MEXICO:* Santa Fe, April 10-11. Sec., Dr. LeGrand Ward, 141 Palace Ave., Santa Fe.
NEW YORK: Albany, Buffalo, New York City and Syracuse, June 26-29. Sec., Dr. R. R. Hannon, Education Bldg., Albany.
NORTH DAKOTA: Grand Forks, July 5-8. Sec., Dr. G. M. Williamson, 4½ S. Third St., Grand Forks.
OHIO: *Endorsement.* Columbus, April 4. Sec., Dr. H. M. Platter, 21 W. Broad St., Columbus.
OREGON:* *Endorsement.* Portland, April 22. Exec. Sec., Miss L. M. Conlee, 608 Failing Bldg., Portland.
RHODE ISLAND:* Providence, April 6-7. Chief, Division of Examiners, Mr. Thomas B. Casey, 366 State Office Bldg., Providence.
SOUTH CAROLINA: Columbia, June 26-28. Sec., Dr. N. B. Heyward, 1329 Blandena St., Columbia.
TEXAS: Houston, March 22-24. Final date for filing application is March 10. Sec., Dr. T. J. Crowe, 918-20 Texas Bank Bldg., Dallas.
WEST VIRGINIA: Charleston, May 1-3. Commissioner, Public Health Council, Dr. John E. Offner, State Capitol, Charleston.
WISCONSIN:* Milwaukee, June 27-29. Sec., Dr. C. A. Dawson, Tremont Bldg., River Falls.

* Basic Science Certificate required.

BOARDS OF EXAMINERS IN THE BASIC SCIENCES

ARKANSAS: Little Rock, March 6. Sec., Mr. L. E. Gebauer, 701 Main St., Little Rock.
COLORADO: Denver, March 8-9. Sec., Dr. E. B. Starks, 1459 Ogden St., Denver.
DISTRICT OF COLUMBIA: Washington, April 17-18. Sec., Commission on Licensure, Dr. G. C. Ruhland, 6150 E. Municipal Bldg., Washington.
FLORIDA: Gainesville, June 8. Sec., Dr. J. F. Conn, John B. Stetson University, DeLand.
IOWA: Des Moines, April 11. Dir., Division of Licensure and Registration, Mr. H. W. Grefe, Capitol Bldg., Des Moines.
MICHIGAN: Ann Arbor and Detroit, May 12-13. Sec., Miss Eloise LeBeau, 101 N. Walnut St., Lansing.
MINNESOTA: Minneapolis, April 4-5. Sec., Dr. J. C. McKinley, 126 Millard Hall, University of Minnesota, Minneapolis.
NEBRASKA: Omaha, May 2-3. Dir., Bureau of Examining Boards, Mr. Oscar F. Humble, 1009 State Capitol Bldg., Lincoln.
OREGON: Portland, March 4. Sec., Board of Higher Education, Mr. C. D. Byrne, University of Oregon, Eugene.
SOUTH DAKOTA: Vermillion, June 4-5. Sec., Dr. G. M. Evans, Yankton.
WISCONSIN: Madison, April 1. Sec., Prof. R. N. Bauer, 152 W. Wisconsin Ave., Milwaukee.

Bureau of Legal Medicine and Legislation

MEDICOLEGAL ABSTRACTS

Optometry Practice Acts: Illegality of Corporate Practice.—Beiling, who was licensed to practice optometry in Kentucky, was employed on a salary and bonus basis by the Kay Jewelry Company, a corporation. He had exclusive control of the optical department in the corporation's store, and his professional judgments and acts were not interfered with by the corporation. He made examinations and tests of customers of the store and prescribed such lenses as he deemed necessary. The lenses so prescribed were manufactured by another company and forwarded to the corporate employer. Beiling would then fit the glasses on the so-called patient. All fees and charges were paid directly to the corporation, which kept the records and accounts. The corporation advertised this department as "Our Modern Optical Department," sometimes naming Beiling as its employed optometrist and sometimes not mentioning him at all.

The Kentucky optometry practice act specifically authorizes the revocation of the license of any licentiate who abets in the practice of optometry any person not holding a license to practice optometry. The state board of health, acting on the hypothesis that Beiling was abetting the Kay Jewelry Company to practice optometry, after notice and hearing, ordered his license to practice optometry revoked, and the governor of the state affirmed the board's action. Beiling then brought an action in the circuit court, Jefferson County, chancery branch, first division, to enjoin the board of health and its members from revoking his license. From an order of the trial court granting him the relief he asked, the defendants appealed to the Court of Appeals of Kentucky.

The order of the circuit court enjoining the revocation of Beiling's license was based on the express reasoning of the court that the purpose of the optometry practice act was to protect the public from unskilled persons examining and prescribing for eyes, that that purpose was met when the person so practicing had been licensed, and that as the Kay Jewelry Company acted only through its agent, Beiling, and did nothing which could be deemed to be the practice of optometry other than what Beiling did, it followed that the Kay Jewelry Company did not practice optometry and that consequently when Beiling, acting individually, collaborated with himself acting as its agent, he was not aiding or abetting the jewelry company to practice optometry. With this reasoning and conclusion the Court of Appeals disagreed. While a corporation, said the court, is a person for many purposes, it cannot be licensed to practice a learned profession, which can only be done by an individual who has received a license to do so after proving his qualification and knowledge of the subject. Thus, there is scarcely any judicial dissent from the proposition that a corporation cannot lawfully engage in the practice of law, medicine, dentistry or any of the limited healing arts. 41 Am. Jur., Physicians and Surgeons, Sec. 20. It seems that the less the personal equation enters into the particular practice, or the farther the service of the practitioner is removed from a personal relationship of trust and confidence and from the exercise of individual ability and talent, the more liberal becomes the judicial view as to the power of a corporation, or other entity not capable of being licensed itself, to carry on a profession or business through licensed individual employees. In the matter of the practice of optometry, the courts of the several jurisdictions are divided. Notes 141 A. L. R. 888. It will be found that most of the cases which hold in effect that an employer does not practice optometry through an employed licensed optometrist are distinguishable from those which hold to the contrary by differences in the terms of the statutes involved, which differences may relate to specific or implicit provisions, and in the particular facts. 41 Am. Jur., Physicians and Surgeons, Sec. 28. In some of the cases the character of the relationship between the corporation and the practitioner was controlling. Thus it is held that where only the relation of landlord and tenant exists, as where a licensed optometrist has his office in a store and the proprietor advertises that such a practitioner is available to its customers, the relation is legitimate. *Rowe* v. *Burts, Inc.*, Ohio App., 31 N. E. (2d) 725. But it may be unlawful with additional or different conditions. *State* v. *Goldman Jewelry Co.*, 142 Kan. 881, 51 P. (2d) 995, *Neill* v. *Gimbel Bros.*, 330 Pa. 213, 199 A. 178. In the case at bar the court thought it particularly significant to consider the language of the Kentucky statute defining the practice of optometry, which read as follows:

"(*a*) 'Practice of optometry' means the examination of the human eye without the use of drugs, medicines or surgery to ascertain the presence of defects or abnormal conditions that can be corrected by the use of lenses, prisms or ocular exercises and their adaptation for the aid thereof and the correction or attempt to correct defects of the eye by any means, except upon the prescription of a physician.

"(*b*) Opening an office, or announcing to the public a readiness to do any of the acts mentioned in this subsection constitutes practicing optometry.

"(*c*) The practice of optometry does not include the sale of spectacles, eyeglasses or lenses only as merchandise in a duly established mercantile establishment." (KRS 311.010).

In this case, the court continued, the corporation did more than sell eyeglasses and lenses as merchandise. Its acts here clearly came within the purview of the statute just quoted in view of the specific provision of the statute declaring that the opening of an office and announcing a readiness to render the services of an optometrist constitutes practicing optometry. We are of the opinion, therefore, that the corporation was engaged in the practice of optometry within the meaning of the statute.

We cannot accept, the court continued, the premise of the argument or agree with the reasoning of the trial court that the corporation did nothing which can be regarded as practicing optometry other than what its employee did or that he was only acting as an individual in collaboration with himself as an agent. Surely the doctrine of respondeat superior would have applied had he committed a tort in and during the course of his employment. Optometry was one of the corporation's departments of business, and Beiling was its agent. His services are clearly within the meaning of aiding and abetting it in carrying on that business of which his professional services were only a necessary part. The essential element of aiding and abetting the commission of any act is assisting and taking an active part in it. Certainly, Beiling did that in the unlawful practice by his employer. We are of the opinion, therefore, continued the court, that the lower court should have refused to set aside the order of revocation of the state board of health. For the reasons stated the order of the state board of health, in effect, revoking Beiling's license to practice optometry was affirmed.—*Kendall v. Beiling, 175 S. W. (2d) 489 (Ky., 1943).*

Society Proceedings

COMING MEETINGS

Alabama, Medical Association of the State of, Montgomery, April 18-20. Dr. D. L. Cannon, 519 Dexter Avenue, Montgomery, Secretary.
Arizona State Medical Association, Phoenix, April 14-15. Dr. Frank J. Milloy, 112 N. Central Ave., Phoenix, Secretary.
Arkansas Medical Society, Little Rock, April 17-18. Dr. W. R. Brooksher, 602 Garrison Avenue, Fort Smith, Secretary.
Association of State and Territorial Health Officers, Washington, D. C., March 20-23. Dr. G. C. Ruhland, 300 Indiana Ave., N.W., Washington, D. C., Secretary.
Conference of State and Provincial Health Authorities of North America, Washington, D. C., March 22. Dr. A. J. Chesley, State Office Building, St. Paul, Minn., Secretary.
Florida Medical Association, St. Petersburg, April 13-14. Dr. Shaler Richardson, 111 West Adams St., Jacksonville, Secretary.
Iowa State Medical Society, Des Moines, April 21-22. Dr. Robert L. Parker, 3510 Sixth Avenue, Des Moines, Secretary.
Maryland, Medical and Chirurgical Faculty of, Baltimore, April 25-26. Dr. W. Houston Toulson, 1211 Cathedral St., Baltimore, Secretary.
Minnesota State Medical Association, Rochester, April 13-15. Dr. B. B. Souster, 493 Lowry Medical Arts Bldg., St. Paul, Secretary.
Missouri State Medical Association, Kansas City, April 23-25. Mr. Raymond McIntyre, 634 N. Grand Blvd., St. Louis, Executive Secretary.
New Jersey, Medical Society of, Atlantic City, April 25-27. Dr. Alfred Stahl, 55 Lincoln Park, Newark, Secretary.
New Orleans Postgraduate Medical Assembly, New Orleans, March 6-9. Dr. Joseph S. D'Antoni, 1430 Tulane Ave., New Orleans 13, Secretary.
Northern Tri-State Medical Association, Toledo, Ohio, April 11. Dr. Oscar P. Klotz, 127 W. Hardin St., Findlay, Ohio, Secretary.
Oklahoma State Medical Association, Tulsa, April 24-26. Dr. L. J. Moorman, 1200 N. Walker St., Oklahoma City, Secretary.
Tennessee State Medical Association, Nashville, April 11-13. Dr. H. H. Shoulders, 706 Church St., Nashville, Secretary.

Current Medical Literature

AMERICAN

The Association library lends periodicals to members of the Association and to individual subscribers in continental United States and Canada for a period of three days. Three journals may be borrowed at a time. Periodicals are available from 1934 to date. Requests for issues of earlier date cannot be filled. Requests should be accompanied by stamps to cover postage (6 cents if one and 18 cents if three periodicals are requested). Periodicals published by the American Medical Association are not available for lending but can be supplied on purchase order. Reprints as a rule are the property of authors and can be obtained for permanent possession only from them.

Titles marked with an asterisk (*) are abstracted below.

American Journal of Diseases of Children, Chicago

66:597-728 (Dec.) 1943

Encephalitis Complicating Measles. H. A. Reisman and A. S. Rosen.—p. 597.
Ultraviolet Irradiation of Blood in Treatment of Experimental Poliomyelitis. J. A. Toomey and W. S. Takacs.—p. 605.
Uniformity of Riboflavin Content of Milk Produced Under Standardized Conditions. A. D. Holmes and Julia O. Holmes.—p. 607.
*Acquired Syphilis in Infants and in Children: Report of 3 Cases. G. W. Creswell, Elizabeth Seech and Willa L. Murray.—p. 611.
Folds and Creases of Skin During Childhood. E. Nassau.—p. 615.
Poliomyelitis: I. Basic Considerations Needed for Judging Therapeutic Results. J. A. Toomey.—p. 635.

Acquired Syphilis in Infants and Children.—Creswell and his collaborators show that syphilis may be acquired by extremely young children. They report 3 cases of their own observation. A number of boarders in the home were suspected of being the source of the syphilitic infection of the first child. An aunt with an extremely infectious form of untreated syphilis was the source of infection of the second and third children, who were siblings. Primary lesions are frequently unrecognized in infants with acquired syphilis. The disease in 1 sibling should arouse a suspicion of acquired syphilis if there is no evidence of the mother's having or having had syphilis. Since the risk of subsequent development of syphilis of the cardiovascular c the central nervous system is greater in infants with acquired syphilis than in those with congenital syphilis, emphasis must be placed on the importance of alertness to the discovery of this type of disease. All lesions should be carefully noted and followed systematically by a Wassermann test as a means of prevention of subsequent, more serious, difficulties. Infants in whom the disease is diagnosed early have a more favorable prognosis as to cure. Complete studies of the families should be made in all such cases to insure prompt location of infected persons and early therapy. Overcrowding of rooms, lack of adequate sanitation and poor economic conditions with accompanying lowered moral standards play a definite part in the spread of this type of disease.

American Journal of Ophthalmology, Cincinnati

26:1251-1356 (Dec.) 1943

Endophthalmitis Due to B. Subtilis Following Injury. A. B. Reese and D. Khorazo.—p. 1251.
Study of Mustard Gas Lesions of Eyes of Rabbits and Men. Ida Mann and B. D. Pullinger.—p. 1253.
Oral Use of Prophylactic Sulfadiazine for Cataract Extractions. J. S. Guyton and A. C. Woods.—p. 1278.
Is Glaucoma a Deficiency Disease? Important Details Concerning the Nonsurgical Treatment of Glaucoma Simplex. M. J. Schoenberg.—p. 1282.
Ocular Findings in Feebleminded Male Castrates. R. G. Scobee.—p. 1289.
Choked Disks and Low Intrathecal Pressure Occurring in Brain Tumor. P. J. Leinfelder.—p. 1294.
*Relationship of Orthoptic Treatment to Surgery. A. DeH. Prangen.—p. 1298.
Cylinder Retinoscopy Simplified. J. I. Pascal.—p. 1304.
Evaluation of Orthoptic Instruments. Elizabeth K. Stark.—p. 1308.

Orthoptic Treatment and Surgery in Strabismus.—According to Prangen, restoration of function is the dominant purpose in the treatment of strabismus, and the connecting link between cosmetic surgery and restoration of normal function appears to be orthoptic training. Orthoptic training should be continued as long as satisfactory and definite progress is being made. The value of orthoptic training in any given case cannot be established in a few months. In some of the most successful cases at the Mayo Clinic, continuous training has been given for several years. In selected cases and under favorable circumstances training can be carried out for from three to five years with good results. In most cases, however, operation should be performed much sooner than this, and further training should be given subsequently. The ideal procedure would seem to be a preliminary period of orthoptic training, then operation, and further training. Too often, after a successful operation has been performed and the eyes appear to be straight, the family and the surgeon lose interest and further treatment is not given. In a comparison of the results of orthoptic training and operation in the treatment of strabismus, it would appear that one is as important as the other, and, if to these forms of treatment accurate refraction is added, three weapons will be at hand for the combating of strabismus. It is difficult to say which of the three is the most indispensable.

Annals of Allergy, Minneapolis

1:185-270 (Nov.-Dec.) 1943

*Allergic Bronchitis. J. W. Thomas and R. V. Taylor.—p. 185.
Ntthamine Hydrochloride and Theophylline Isobutanolamine in Treatment of Nasal Allergy and Asthma. F. K. Hansel.—p. 199.
Chemistry of Ragweed Pollen Extract: IV. Some Chemical Observations on Decolorized Ragweed Pollen Extract. E. A. Brown and N. Benotti.—p. 208.
Normal Adult Human Pulse Rate. A. F. Coca.—p. 212.
*Diagnosis and Treatment of Food Allergies Through Propeptans. E. Urbach.—p. 219.
Food Allergies and Vitamin C. H. N. Holmes.—p. 235.

Allergic Bronchitis.—Allergic bronchitis is a perennial or seasonal allergic reaction to sensitizing substances in a susceptible individual. It is characteristized by a chronic recurring or paroxysmal cough, which usually occurs in the absence of upper respiratory infection or intrathoracic disorder. In a series of 2,033 consecutive admissions to the Department of Allergy at the Cleveland Clinic there were, according to Thomas and Taylor, 244 patients, or 12 per cent, with a diagnosis of allergic bronchitis. For the general population this would amount to an incidence of between 1 and 3 per cent. The primary symptom of chronic dry cough may be accompanied by blood streaked sputum, expectoration of mucoid or mucopurulent sputum, wheezing, dyspnea, frequent colds, fever, fatigue, loss of weight, anorexia, chest pain, sweating, hoarseness, and aggravation of cough with exertion. Diagnosis is primarily the exclusion of all other possibilities. A family history of allergy and other personal manifestations of allergy may indicate the diagnosis, but lack of them does not exclude it. Every patient received complete scratch and intradermal tests except for the pollens, which were tested only when the history suggested a seasonal factor. While most of the causative allergens were inhalant, a few were foods. The high incidence of fungi and mold sensitivity in this series is probably indicative of strong antigens and also of a high incidence of epidermophytosis. Treatment consists of a proper allergy regimen after adequate studies. It will usually prevent complications such as asthma, emphysema and bronchiectasis. Only 15 per cent of the cases showed no response to allergy management. Best results are obtained with persons under 30 years of age, with symptoms of less than three years' duration. Most favorable results were obtained by patients with a high blood eosinophilia and those with a positive family history of allergy. Conversely, poor results are more apt to be obtained by patients in the older age groups with symptoms of over five years' duration and with no hereditary factors and no eosinophilia.

Propeptans in Food Allergies.—Propeptans are protein derivatives obtained from individual animal and vegetable food proteins by digestion with hydrochloric acid, pepsin and trypsin, which, however, retain the specificity of the corresponding proteins. Urbach shows that propeptans are of value both in diagnosis and in treatment of food allergy. Identification of the responsible foods can be readily achieved by the propeptan diet, i. e. by giving type specific propeptans forty-five minutes prior to the corresponding foods. If the objective and subjective manifestations are relieved by this diet, withdrawal of one of the propeptans every second day, while the respective food item is still ingested, will detect hypersensitiveness to any one or more of the nutritional allergens in question. After the identity of the food allergen has been established, specific propeptan therapy will deallergize a patient with food sensitiveness

in two or three weeks. If the offending foods have not been determined or if it is felt that it is not essential that they be known, a polypropeptan regimen may be instituted. Polypropeptan is a mixture of twelve specific food propeptans and protects, therefore, only against these twelve specific food items.

Archives of Neurology and Psychiatry, Chicago

50:633-758 (Dec.) 1943

*Chemotherapy of Intracranial Infections: II. Clinical and Pathologic Effects of Intracranial Introduction of Sulfanilamide, Sulfathiazole and Sulfadiazine in Normal Dogs. W. F. Meacham, R. Angelucci, E. Benz and C. Pilcher.—p. 633.
Electric Convulsive Therapy, with Emphasis on Importance of Adequate Treatment. L. B. Kalinowsky.—p. 652.
Monilemia Associated with Toxic Purpura: Report of Case. A. Wikler, E. G. Williams and C. Wiesel.—p. 661.
Aneurysm of Circle of Willis Associated with Congenital Polycystic Disease of Kidneys. F. M. Forster and B. J. Alpers.—p. 669.
Diffuse Hypertrophy of Cerebellar Cortex (Myelinated Neurocytoma): Report of Case. D. Duncan and S. R. Snodgrass.—p. 677.
Combined Convulsive Therapy and Psychotherapy of Neuroses. J. D. Moriarty and A. A. Weil.—p. 685.
Perceptual-Motor Patterns Following Bilateral Prefrontal Lobotomy. G. W. Kisker.—p. 691.
*Use of Insulin as Sedation Therapy: Control of Basic Anxiety in Psychoses. T. A. C. Rennie.—p. 697.

Chemotherapy of Intracranial Infections.—Meacham and his associates studied the clinical and pathologic effects of sulfanilamide, sulfathiazole and sulfadiazine on the brain and its coverings in one hundred and fifteen experiments on dogs. These compounds were implanted intracranially by various methods and in various amounts. When placed on the intact cerebral cortex sulfathiazole produced convulsions, and all three of the preparations produced pleocytosis. Pathologic effects were (1) immediate acute pachymeningitis and leptomeningitis, with corresponding subacute or chronic inflammation in the later stages, (2) pronounced fibroplasia in the dura, (3) conspicuous gliosis in the cortex and (4) varying degrees of neuronal degeneration, proliferation of oligodendrogliocytes and metamorphosis of microglia cells. All reactions were least extensive when sulfanilamide was employed and increased with all the drugs when the dose was increased. These experiments do not indicate that the effects of sulfanilamide and sulfadiazine are sufficiently harmful to contraindicate their critical use in the therapy of intracranial infections. They suggest that sulfathiazole should never be employed in a cranial wound in which there is an opening in the dura.

Insulin as Sedation Therapy.—According to Rennie, the use of insulin for the production of coma in the therapy of psychoses has not fulfilled the expectations of a few years ago. Electric shock seems likely to replace insulin. He directs attention to the effectiveness of insulin in subcoma doses. He employed this modified type of insulin therapy in the management of 28 cases. Treatment was given six days a week, the dose starting with 10 units of insulin and being increased 10 units daily until the amount was reached which produced deep sleep from which the patient could still be aroused with strong stimuli. Usually 50 to 90 units sufficed. Nineteen of the 28 patients showed great clinical improvement, clearly justifying the method. Four others displayed some improvement. Only 5 derived no benefit. The patients who showed improvement included persons with schizophrenic excitement, panic, catatonic stupors, hebephrenic dilapidation, suicidal depressions, depression with definite aversion and manic excitement. The therapy produced relaxation, reduced inner tension and relieved anxiety and fear. It prepared the patient for psychotherapy. Active psychotherapy was carried out hand in hand with the administration of insulin. The author concludes that the administration of insulin in subcoma doses provides an effective method of sedation. Its specific action seems to be in alleviation of anxiety. With relief of anxiety the psychotic manifestations sometimes rapidly disappear. The method is entirely safe and is far superior to that achieved by chemical sedation.

Bulletin New York Academy of Medicine, New York

19:815-880 (Dec.) 1943

Serum Proteins in Relation to Liver Disorders. J. Post and A. J. Patek Jr.—p. 815.
Diagnostic Significance of Serum Alkaline and Acid Phosphatase Values in Relation to Bone Disease. H. L. Jaffe and A. Bodansky. —p. 831.

Indiana State Medical Assn. Journal, Indianapolis

37:1-56 (Jan.) 1944

*Chronic Undulant Fever of Swine Origin as an Important Public Health Problem. T. B. Rice.—p. 1.
Pentothal Sodium: Range of Usefulness, Complications and Their Management. G. J. Thomas.—p. 5.
Treatment of Acute Suppurative Otitis Media by Local Sulfonamide Therapy: Report of 84 Cases. M. E. Miller.—p. 11.
Surgical Treatment of Varicose Veins. R. W. Lamb.—p. 13.
Anesthesia of Protoplasm. F. H. Kelly.—p. 17.
Rabbit Antiserum Against Influenza A and B Viruses for Inhalation Prophylaxis Against Epidemic Influenza. H. M. Powell.—p. 18.

Undulant Fever of Swine as Health Problem.—In man the porcine form of undulant fever is more severe than the bovine type. The infection can be contracted by handling the diseased hog in the living state or by handling the flesh of the diseased hog when it has just been killed. As this germ is not easily killed by drying, there is reason to believe that the dust or the mud in the hog lot may also be a source of infection. The porcine form of disease in human beings is essentially an occupational disease. Many veterinary surgeons have been ill of this disease at one time or another. Butchers are the second group of persons in whom the disease is occupational and farmers are the third group. The disease is rather common among farmers, although it has many times been called malaria, typhoid, "walking typhoid," bilious fever, arthritis, rheumatism, tuberculosis, general "rundown" condition and many other names. The chronic form particularly is frequently not recognized and may be considered general ill health or a neurosis. It is a public health problem in hog raising states. The satisfactory control of undulant fever is dependent on the control and elimination of brucellosis in farm animals. The author suggests the desirability of immunization of exposed persons.

Journal of Immunology, Baltimore

47:439-596 (Dec.) 1943

Antepartum Transmission of Lymphogranuloma Venereum Antibodies and Their Duration in Infant. Sonnia Levine, J. G. M. Bullowa and I. E. Scheinblum.—p. 439.
Immunochemistry of Allergens. V. Comparison of Rates of Dialysis of Crystalline Ovalbumin and of Cottonseed Allergen CS-1A. E. J. Coulson, J. R. Spies and H. Stevens.—p. 443.
Studies on Immobilization Reaction of Trichomonas Foetus (Protozoa) in Cattle. B. B. Morgan.—p. 453.
*Additional Variants of Rh Type Demonstrable with Special Human Anti-Rh Serum. A. S. Wiener and Eve B. Sonn.—p. 461.
*Group Specific Substances in Saliva of Newborn. A. S. Wiener and Ruth B. Belkin.—p. 467.
Prophylactic Immunization Against Carrión's Disease. C. Howe and M. Hertig.—p. 471.
Reaction of Smooth Muscle of Denervated Iris in Anaphylaxis: Comparative Study in Guinea Pig, Rabbit, Dog, Cat and Monkey. M. B. Dender.—p. 483.
Influence of Environmental Temperature and Vitamin Deficiency on Phagocytic Functions. Esther Cottingham and C. A. Mills.—p. 493.
Phagocytic Activity as Affected by Protein Intake in Heat and Cold. C. A. Mills and Esther Cottingham.—p. 503.
Relation of Dose of Antigen to Degree of Anaphylactic Shock in Dogs. C. A. Dragstedt.—p. 505.
Method for Increasing Combining Power of Tetanal Toxin. W. L. Koerber, W. E. Bunney and Gertrude E. Mook.—p. 507.

Variants of Rh Type.—Among Rh positive bloods two major subdivisions have been identified, designated as Rh_1 and Rh_2. Recently Wiener and Sonn encountered a new variety of human anti Rh serum, by means of which further major subdivisions of the Rh type can be demonstrated. They describe the properties of this special anti Rh serum and some observations on the distribution and heredity of the agglutinogen detected by it. The serum described was from the mother of an erythroblastotic baby. In addition to the usual anti Rh agglutinins it contains a special agglutinin of high titer which agglutinated only about one third of all bloods. The agglutinin in question proved to be a special type of anti Rh agglutinin reacting with about three fourths of Rh_2 bloods and only about one fourth of Rh_1 bloods. The special agglutinogen detected by the serum is apparently inherited as a simple mendelian dominant, presumably due to the action of a special allelic gene.

Group Specific Substances in Saliva of Newborn.—Wiener and Belkin point out that, as first demonstrated by Lehrs and Putkonen, human beings fall into two classes, secretors and nonsecretors, depending on the presence or absence of the group specific substances in secretions. For distinguishing the two types the usual practice is to test saliva, because of its

strong reactivity and the ease with which it can be obtained. Schiff and Sasaki found that the secretor character is inherited as a simple mendelian dominant by means of a pair of allelic genes. Accordingly 2 persons who are nonsecretors can have no children who are secretors. While the chance that 2 parents would both be nonsecretors is small, still there could be rare cases of disputed parentage in which this test might be of some help. It is important to establish whether or not the secretor character is as sharply defined in the newborn as in adults. Hartmann states that the distinction between the two types is not sharp in infants. The authors investigated this problem on thirty pairs of saliva samples from mothers and their newborn infants. It was found that the distinction between secretors and nonsecretors was as sharp in the infants as in the mothers, indicating that this character is fully developed at birth and contradicting the report of Hartmann.

New England Journal of Medicine, Boston

229:885-918 (Dec. 9) 1943

Studies in Diabetes Mellitus and Transient Glycosuria in Selectees and Volunteers. H. Blotner and R. W. Hyde, with assistance of L. V. Kingsley.—p. 885.
Current Considerations of Army Anesthesiologist. S. J. Martin.—p. 893.
Grave Infections of the Hand. J. E. Flynn.—p. 898.

229:919-958 (Dec. 16) 1943

Cervical Cord Injuries: Study of 101 Cases. D. Munro.—p. 919.
*Purpura Fulminans (Waterhouse-Friderichsen Syndrome): Report of Case with Recovery. S. D. Peabody.—p. 934.
Instrumental Removal of 2½ Pound Bladder Calculus, with Recovery. F. J. Lepreau Jr. and R. H. Jenkins.—p. 937.
Curable Forms of Heart Disease. A. S. Freedberg and H. L. Blumgart, —p. 939.

Purpura Fulminans (The Waterhouse-Friderichsen Syndrome).—The Waterhouse-Friderichsen syndrome—adrenal hemorrhage associated with purpura—is also known as acute hemorrhagic adrenalitis, suprarenal apoplexy and purpura fulminans. The exact cause of the disease is not known, and recovery is rare. Peabody observed the disease in a girl aged 19 whose history he relates in detail, because she recovered. The condition is now more frequently recognized clinically. Any patient, especially a young child, who develops spontaneously or in the course of a contagious disease cyanosis, purpuric eruption, profound shock and hyperpyrexia should be regarded as manifesting the syndrome. Since the course of this disease is often rapid and fulminating, a prompt diagnosis followed by early and active treatment is imperative. In view of the high mortality, heroic measures seem justified. Since the infection is usually bacterial in origin, the sulfonamides seem to be the mainstay of therapy. Hormonal replacement with both adrenal cortex extract and epinephrine are indicated in the hope of carrying the patient along until resumption of adrenal function takes place. Plasma, blood transfusions and other supportive therapy may be indicated.

Public Health Reports, Washington, D. C.

58:1837-1880 (Dec. 17) 1943

Influence of *p*H and Temperature on Survival of Coliforms and Enteric Pathogens When Exposed to Free Chlorine. C. T. Butterfield, Elsie Wattie, S. Megregian and C. W. Chambers.—p. 1837.

Western J. Surg., Obst. & Gynecology, Portland, Ore.

51:463-514 (Dec.) 1943

Changing Concepts in Physiology of Female Sex Hormones: Presidential Address. C. F. Fluhmann.—p. 463.
Extraperitoneal Cesarean Section. H. C. Stearns.—p. 468.
Method of Wound Closure in Transverse Abdominal Incisions. A. V. Petit.—p. 479.
Excretion Rates of Histidine in Pregnant and Nonpregnant Women. E. W. Page.—p. 482.
Unusual Case of Abdominal Pregnancy. K. L. Schaupp.—p. 491.

Wisconsin Medical Journal, Madison

42:1213-1304 (Dec.) 1943

Some Clinical Aspects of Bronchiogenic Carcinoma. G. C. Owen. —p. 1233.
Anesthesia Today. J. S. Lundy, R. C. Adams and T. H. Seldon. —p. 1235.
Treatment of Meningococcic Meningitis. Annette C. Washburne. —p. 1239.
Medical Control of Poisons in Industry. E. L. Belknap.—p. 1246.

FOREIGN

An asterisk (*) before a title indicates that the article is abstracted below. Single case reports and trials of new drugs are usually omitted.

British Medical Journal, London

2:633-666 (Nov. 20) 1943

Social Medicine: Its Meaning and Its Scope. J. A. Ryle.—p. 633.
*Therapeutic Value of Gas Gangrene Antitoxin. M. G. MacFarlane.—p. 636.
Dyspepsia: An Investigation. H. Edwards and W. S. C. Copeman. —p. 640.
Bacteriology of Brain Abscess. A. M. McFarlan.—p. 643.
Handling of Small Biopsy Material. A. C. Lendrum.—p. 644.

Gas Gangrene Antitoxin.—The survey by MacFarlane is based on the reports of anaerobic wound infections received by the Medical Research Council. The object of the present analysis was to find out whether antitoxin was of any value in treatment by comparison of the fatality rates of treated and untreated cases. The reports received fell into three series: 88 reports on casualties which occurred in May and June 1940, before and during the Dunkirk battle; 85 reports on casualties in the Middle East forces from 1940 to 1943, and 165 reports of anaerobic wound infections from other theaters of war. The third group is analyzed in greater detail. The criterion of gas gangrene taken for inclusion of a case in this analysis—the presence of pronounced toxemia—was noted in 139 cases (85 per cent). The fatality rate was significantly lower among the patients who received antitoxin, and this difference between treated and untreated cases persisted in those who received major surgical treatment, including a group in which the site of primary infection was rapidly extirpated by amputation. The combined use of surgery and antitoxin was therefore more effective than that of surgery alone. The effect of antitoxin was more pronounced in those who received the initial therapeutic dose soon after diagnosis, but this difference was probably due not only to the speed of administration but also to the fact that a greater proportion of the patients in this group received a large total dosage (50,000 units or more) of antitoxin. The fatality rate of the patients who received no major surgical treatment was nearly 100 per cent, and in the cases reported here the rate in this group was not reduced by antitoxin therapy. Patients in whom the site of the gas gangrene involved the thigh, buttocks or abdomen showed a poorer response to antitoxin than those in whom the site was more favorable to the elimination of the infection. These results emphasize the necessity for the early and combined use of surgery, effective chemotherapy and antitoxin in the treatment of gas gangrene.

2:667-702 (Nov. 27) 1943

Three Skin Diseases in Wartime. H. MacCormac.—p. 667.
Visual Physiology of Cinema. G. H. Bell.—p. 669.
*Encephalomyelitis Following Vaccination in Fife. G. M. Fyfe and J. B. Fleming.—p. 671.
Pheniodol: New Contrast Medium for Cholecytography. F. H. Kemp. —p. 674.
Case of Conversion Hysteria. R. West.—p. 676.

Encephalomyelitis Following Vaccination.—Fyfe and Fleming report three outbreaks of smallpox in Scotland during 1942. The vaccinal state of the public was low. It was estimated that in one town less than 30 per cent and in another less than 50 per cent of the population had been vaccinated. Free vaccination was offered and 54,698 doses of lymph were issued by the county public health department. Postvaccinal disorders were of comparatively brief duration, and, although no reliable evidence was forthcoming that vaccination had in general a deleterious effect on health, the occurrence of 9 cases of encephalomyelitis following vaccination gave rise to disquietude. Eight of these occurred among 52,772 and the other case among 20,179 vaccinations. This makes the incidence in the first group unusually high, 1 in 6,600. The case mortality was 44 per cent. In 6 of the cases symptoms were entirely of cerebral origin and in 2 they were of spinal origin, apparently an uncommon manifestation. In 1 the symptoms were predominantly meningeal. Immune serum was used in the serious cases. There was not enough evidence to make a decision regarding the value of antivaccinial horse serum. It was fortunate that the parents had been revaccinated about the same time as their

children. Parental immune serum proved to be of great value when given in large doses, e. g. 140 cc. It can be given without serious risk of serum reaction. It is suggested that there may be a liability to onset of encephalomyelitis in unvaccinated persons suffering from acute infections of the upper respiratory tract. Vaccination is urged in infancy in view of the risk of involvement of the nervous system in later years. If primary vaccination of children becomes unavoidable, steps should be taken to secure a source of immune serum as a precaution.

2:703-736 (Dec. 4) 1943

Human Response to Flying Stress. C. P. Symonds.—p. 703.
Diphtheria Alum-Precipitated Toxoid: Observations on Immunity. Response in Human Subject to Varying Lf Dosage Combinations. G. Bousfield.—p. 706.
*Duration of Artificial Active Immunity Against Diphtheria. H. L. Duke and W. B. Stott.—p. 710.
Gunshot Wound of Innominate Artery. G. F. Langley.—p. 711.
Tuberculosis in London. W. A. Daley and B. Benjamin.—p. 712.

Duration of Artificial Immunity Against Diphtheria.—Duke and Scott report an investigation into the duration of artificial immunity against diphtheria in a country area with a child population (1 to 15 years) of 9,600, of whom 95 per cent had been immunized. Over 3,000 children were Schick tested two to six years after completion of a course of immunization. None of these were positive when tested three to six months after the course. The number of treated children who lose their immunity to diphtheria increases steadily with the passing of time, rising from 4 per cent after two years to 18 per cent after six years. The figures should be compared with the results obtained by the routine testing three to six months after the completion of the course of all inoculated children, i. e. 2 per cent primary failures. The incalculable factor in the interpretation of these figures is the degree to which natural immunizing processes operate. Among the children of large cities natural processes may result in 50 to 70 per cent of school children becoming naturally Schick negative. The "under fives" in their rural region failed to reveal evidence of natural immunizing processes. Certain feebly positive children, when tested again six months or later and without any further treatment, were found to have become negative. The so-called carrier menace is the favorite target for the opponents of immunization. These leave it to nature enthusiasts, who, while abusing the immunized carrier, alternately extol and conveniently ignore, according to the angle of their attack, the great body of naturally immune town children, all likewise potential carriers of the bacillus. They ignore too the value of a high carrier rate in a completely immunized child community as a beneficent factor in maintaining the immunity level.

Medical Journal of Australia, Sydney

2:329-348 (Oct. 23) 1943

*Hemoglobin Level in Blood Donors. Lucy M. Bryce and Rachel Jakobowicz.—p. 329.
Swimming Bath Conjunctivitis, with Report of 3 Probable Cases and Note on Its Epidemiology. E. H. Derrick.—p. 334.

Hemoglobin Level in Blood Donors.—Bryce and Jakobowicz reexamined donors after their second and subsequent donations in respect to the hemoglobin content of their blood. The figures presented are based on 18,600 estimations. The hemoglobin level prior to the giving of blood has been estimated in a series of 4,110 men and 8,956 women between the ages of 18 and 65. The average level of hemoglobin was found to be 110.24 per cent in men and 99.47 per cent in women. The average hemoglobin level at different ages was determined in a series of 815 men and 2,603 women. It was lowest in the lowest age group (18 to 30 years) and highest in the highest age group (50 to 65 years) in both men and women. The range was from 108.6 per cent to 109.7 per cent in the men and 96.5 per cent to 101.2 per cent in the women. No significant seasonal variation in hemoglobin level was detected. The hemoglobin level was also estimated in a series of 1,577 men and 3,957 women who had given blood on two or more occasions at intervals of not less than three months. No significant difference was found between the hemoglobin level of men before or after giving blood. In women, 4.14 per cent had a hemoglobin level of less than 85 per cent before giving blood; this figure increased progressively after three or more blood donations to 9.75 per cent of those who had given five or more donations. The authors discuss the factors that influence iron metabolism, particularly in women, and make theoretical estimates of the time required for regeneration after blood donations. They present data gained from detailed observations in 4 cases. The results of iron therapy are shown in 12 cases. In all the cases examined iron therapy has considerably raised the hemoglobin level. The authors emphasize the need for supervision of the hemoglobin level in blood donors and stress the role of iron therapy.

Medicina, Buenos Aires

4:1-108 (Oct.) 1943. **Partial Index**

*Electroencephalogram in Diagnosis of Parathyroid Insufficiency in Man. J. B. Odoriz, E. B. del Castillo, F. J. Manfredi and F. A. de la Balze.—p. 1.
Surgical Therapy of Cancer of Thoracic Esophagus. M. M. Brea.—p. 74.

Electroencephalograms in Parathyroid Insufficiency.—Odoriz and his collaborators obtained electroencephalograms from 17 patients with parathyroid insufficiency. The observed changes were (1) diminution or disappearance of the alpha rhythm in the occipital, parietal or frontal graphs, (2) increase in the frequency and the amplitude of the beta rhythm and (3) appearance of simple spikes and of groups of six or seven slow waves of a frequency of two or three per second, with predominance of frontoparietal waves. The electroencephalogram became normal after correction of the insufficiency by implantation of parathyroids from a human fetus. It remained normal as long as the graft remained active. The hyperpnea test of forty-five minutes demonstrates the changes when they do not appear spontaneously either before correction of insufficiency or after absorption of the graft.

Medicina, Madrid

11:317-396 (Nov.) 1943. **Partial Index**

*Diagnosis of Brucellosis. A. M. Vallejo de Simón and J. F. Egea.—p. 317.
Problem of Malignant Diphtheria. H. Schmidt.—p. 352.
Clinical Considerations on Cases of Preliminary Hydatidosis. P. Piulachs and M. A. Mallén.—p. 367.

Diagnosis of Brucellosis.—According to Vallejo de Simón and Egea, the actual frequency of brucellosis is much higher than that which has been usually reported in the literature. In the last few years 739 cases were observed in the Hospital del Rey (Spain). As the clinical manifestations of the disease are so protean and irregular, diagnosis must rest on laboratory tests. Of these tests the intradermal reaction using Brucella vaccine proved to be the most sensitive. In 107 cases of brucellosis in which it was employed, the skin test was positive in 97.1 per cent. There was no direct correlation between the skin test and the agglutination reaction. In 18 cases (17.3 per cent) a positive intradermal reaction was associated with a negative agglutination reaction, which indicates that the serologic factors responsible for allergic and immunization reactions are different. The skin reaction was tested in 74 cases of various acute and chronic infectious diseases and was found to be negative in all cases. The specificity of the test is thus significantly high. Another advantage was the fact that antibodies responsible for the intradermal reaction appeared earlier and remained longer than agglutinins, which is of great importance for an early diagnosis and for the detection of a past infection. The agglutination reaction was less consistently positive, as compared to the skin test. Agglutinin titers of 1/200 or higher were absolutely specific for infection by Brucella but were present in only 55.7 per cent of a group of 666 cases. If titers of 1/50 or higher are considered significant, the agglutination test was positive in 91.2 per cent of the cases. The opsonocytophagic test, performed according to Huddleson's technic, yielded inconsistent results. Hemoculture in agar-glucose medium is a most specific test but, at the same time, the least sensitive. Of 529 cases of brucellosis only 64 per cent gave a positive hemoculture. The test is inadequate for practical use, for it requires a delicate and difficult technic and, many times, the growth of the organism is slow, yielding positive results only after three to four weeks of culture.

Book Notices

Pioneers of Pediatrics. By Abraham Levinson, B.S., M.D., Associate Professor of Pediatrics, Northwestern University Medical School, Chicago. Second edition. Cloth. Price, $2. Pp. 119, with 29 illustrations. New York: Froben Press, 1943.

In this edition, fresh from the press, Levinson has added new data, and he has recast some of the material contained in the first edition. He has adhered to his original intention to have the book serve as a compendium rather than an exhaustive treatise on pediatric history. The book contains interesting and pertinent descriptions of infantile disorders from the earliest periods of recorded history down to the present era. It is pointed out that in the papyri the sources of the recorded medical knowledge of Egypt are found; as well as directions for the hygienic care and feeding of infants and prescriptions for the treatment of disease. The author traces the origins of pediatric knowledge as it occurs in the Bible and the Talmud. He also briefly refers to the pediatric contributions and writings of the period of Islamic culture as well as the Graeco-Roman period. In several of the succeeding chapters consideration is given to sketches on the pediatric publications contained in the so-called incunabula (volumes published soon after the introduction of printing, 15th century). Among the prominent authors of these early editions were Paulus Bagellardo, an Italian physician, Bartholomaeus Metlinger of Germany and Cornelius Roelin of Belgium. In the 16th century Thomas Phaer, known as the "Father of English Pediatrics," wrote the "Boke of Children." Levinson continues by sketching the careers and contributions of the other pediatric notables during the 17th and 18th centuries.

A glance at this compendium of pediatric history shows that no sustained or systematic studies in this subject were made until the beginning of the 19th century. During the latter period intensive investigations were instituted concerning the anatomy and function of the child's body. As the author points out, it was also at this period that the studies in morbid anatomy began to shed new light on the nature and cause of disease. The author develops the progress of pediatrics during the fruitful and productive years which followed. A series of biographic sketches develop the story of pediatricians and the personalities who made the most important contributions. A number of photographs of the leaders add interest to the descriptive material. This little volume will be read eagerly by those who are interested in the historical development of pediatrics.

Ten Lessons on Meat for Use in Schools. Published by Department of Home Economics, National Live Stock and Meat Board. Sixth edition. Paper. Price, 10 cents. Pp. 138, with illustrations. Chicago, 1943.

This booklet accurately presents an abundance of worthwhile information touching on all aspects of meat consumption. The first few chapters dealing with the nutritive value of meat and its use in the diet have been rewritten to include information on the specific nutritional elements found in meat. Many valuable charts are shown. In subsequent chapters useful information is given with regard to selection of desirable portions of meat and their preservation in the home. The most suitable methods of cooking the various cuts of meat are discussed at considerable length. This treatise carries through to describe the most efficient methods of carving for the many different cuts of meat. The entire booklet contains much material which would prove valuable to any one interested in meat as a food.

The Organization of Permanent Nation-Wide Anti-Aedes Aegypti Measures in Brazil. By Fred L. Soper, D. Bruce Wilson, Servulo Lima and Waldemar Sá Antunes. This report is based on the work of the Cooperative Yellow Fever Service maintained jointly by the Brazilian Government and the International Health Division of the Rockefeller Foundation for eleven years, 1929-1940. Cloth. Pp. 137, with 27 illustrations. New York: Rockefeller Foundation, 1943.

The successful completion of a permanent anti-Aedes aegypti campaign by the combined staffs of the Rockefeller Foundation and the Brazilian government is one of the outstanding accomplishments in disease transmitting insect control. Working in a country where practically every condition is favorable to the Aedes aegypti mosquito, they have developed new technics which made it possible to remove this yellow fever carrying mosquito from the entire nation. Although largely a question of organization and administration, these men and their co-workers found that the mosquito selected certain foci, from which it spread to other areas. By locating these foci and then aggressively applying accepted control measures, it was possible to have more effective results than ever obtained before. Because of their brilliant results they have been prevailed on to describe in great detail all phases of their program. Accordingly, this book presents the details of their anti-Aedes aegypti campaign, which includes the general administrative setup, routine organization of work in urban centers and complementary services in urban areas. There is also the plan of organization for anti-Aedes aegypti measures in the interior, including tables and forms outlined for statistics. There is a chapter devoted to the laws and legal enforcement directives which furnished authority necessary to complete the work. There are detailed instructions on the type of control work used and complete forms for inspection services. In this book any health organization can find all the directives necessary to attempt a permanent mosquito control campaign, especially of the domestic varieties as Aedes aegypti.

The Chemical Front. By Williams Haynes. Cloth. Price, $3. Pp. 264, with illustrations. New York: Alfred A. Knopf, 1943.

Since the time when Slosson began to popularize chemistry for the masses a number of authors, including Henry Holmes, Melville Silverberg, David Dietz, Watson Davis, George Gray and John Ratcliff, have written popular volumes. The present world war has not yet embarked on the use of war gases, but it is nevertheless largely a chemical warfare. Sulfuric acid, chlorine, alcohol, ammonia, toluene and phthalic anhydride are part of the very basis of much that goes on. The synthetic rubber and butadiene are in the lap of the future, and many a chemical plant now engaged in the forces of destruction will be turning to penicillin, plasma, atabrine and plastics. Dr. Williams Haynes, author of "This Chemical Age," has dramatized some of the processes here mentioned. He writes soundly, and his book may well inspire many a young boy to chemistry as a career.

Pain. Proceedings of the Association December 18 and 19, 1942, New York. Editorial Board: Harold G. Wolff, M.D., Chairman, Herbert S. Gasser, M.D., and Joseph C. Hinsey, Ph.D. Research Publications, Association for Research in Nervous and Mental Disease, Volume XXIII. Cloth. Price, $7.50. Pp. 468, with 116 illustrations. Baltimore: Williams & Wilkins Company, 1943.

This volume is an epitome of the most recent data and views on pain. There are thirty-two contributions, which cover the subject of pain from all its angles, namely sensory end organs, afferent fibers and tracts, levels of integrations and pain threshold. Various aspects of clinical pain are discussed in detail. These are head pains, articular disorders, diseases of the eye, genitourinary tract, heart and lungs, gastrointestinal tract and skin, cerebral central pain and pain of the peripheral nerves. Several neurosurgical procedures are described for the relief of pain. This is an excellent book and is highly recommended to all physicians.

Aviation Medicine. By Louis Hopewell Bauer, M.D., Consultant to the Civil Aeronautics Administration and to the Committee on Aviation Medicine of the National Research Council, New York. Edited by Henry A. Christian, A.M., M.D., LL.D., Clinical Professor of Medicine, Tufts College Medical School, Boston. [Reprinted From Oxford Loose-Leaf Medicine with the Same Page Numbers as in That Work.] Cloth. Price, $1.50. Pp. 545-595, with 11 illustrations. New York, London & Toronto: Oxford University Press, 1943.

The author of this book is a flight surgeon who has long been eminently associated with the practical and research science of aviation medicine. Dr. Bauer stresses the fact that aviation medicine is primarily a branch of preventive medicine which is concerned with all the basic sciences. The training requirements and duties of a flight surgeon are given in detail, and it is emphasized that all flight surgeons should fly under all conditions and with all types of pilots in order to be fully aware of problems of aviation medicine at first hand and to have the full confidence of the pilots and their crews.

A brief outline is given of the physical requirements of flying, the necessity for periodic examinations and the physical defects which influence flying ability. In the discussion on the effects of

high altitude on man a statement that 47,000 feet (14 kilometers) is the absolute limit for man even when breathing pure oxygen is no longer true with existing experimental equipment. Unfortunately the sections on aeroembolism and the effects of speed, cold and wind are incomplete from the standpoint of experimental data, most of which, however, are still confidential. The same statement applies to the description of oxygen equipment.

The section on commercial airline flying stresses the need for consideration of poor terrain, heavy passenger load, poor average weather conditions and lack of a copilot when determining the number of hours an airline pilot should fly each month. After the war it is believed that the information in this book can be expanded greatly. The present volume is interesting and useful, particularly to those who are just going into the field of aviation medicine.

Fundamentals of Psychiatry. By Edward A. Strecker, M.D., Sc.D., F.A.C.P., Professor of Psychiatry and Chairman of the Department, Undergraduate School of Medicine, University of Pennsylvania, Philadelphia. New printing. Cloth. Price, $3. Pp. 213, with 15 illustrations. Philadelphia, London & Montreal: J. B. Lippincott Company, 1943.

This book, designed for a popular intelligent audience, makes available complete information regarding current trends in psychiatric thought. The place of psychosomatic medicine in the current trend is made clear. The volume takes up in order the causes of mental disturbances, the classifications, methods of examination, symptomatology, organic, toxic and functional psychoses, with chapters on the psychiatry of the war and the relation of the nurse to the psychiatric patient. The book is clearly not intended for the patient himself or for readers of high school age. It may be especially recommended to the professional reader in medicine, in law, in theology and in similar fields.

Proctology. By Sylvan D. Manheim, M.D., Consulting Proctologist, Rockaway Beach Hospital, Rockaway Beach, N. Y. Oxford Medical Outline Series. Cloth. Price, $2. Pp. 137. New York, London & Toronto: Oxford University Press, 1943.

This "short, concise outline" with blank interleaves apparently was compiled for the author's students and doubtless will be of use to them. Some portions of the outline reflect early books and superseded procedures. The only harm which could come from publication of such a book would be the stimulation of incapable persons to practice proctology, using this imperfect outline as their guide. Although the author feels that his work "should prove of interest to the general practitioner as well as to the student," doubtless he did not intend that it should be used as a working manual by those not trained in proctology.

Blood Supply of the Visual Pathway: A Monograph. By Calvin M. Kershner, A.B., M.D., M.S. Cloth. Price, $3. Pp. 160, with 40 illustrations. Boston: Meador Publishing Company, 1943.

The author has summarized the most important available information on this subject from various sources in the literature. The vascular nutrition and drainage of the nervous tissues from the retina to the calcarine cortex is covered in detail. There are brief discussions of the clinical applications of this knowledge, as in the pictures produced by closure of various vessels. Of the thirty-three illustrations, a few are original but most are from the literature with due acknowledgment. The works of Duke-Elder, Behr, Wolf and Abbie have furnished a large number of these, which are well selected.

A Handbook for Nurse's Aides. By Katherine Tucker Orbison, R.N., M.A., Instructor of Nurse's Aides, American Red Cross. With an introduction by Rufus Cole, M.D., and a foreword by George Baehr, M.D., Chief Medical Officer, United States Office of Civilian Defense. Cloth. Price, $2. Pp. 196, with 96 illustrations by Winifred Pleninger. New York: Devin-Adair Company, 1943.

All over the United States many thousands of women have added to the burdens of their daily lives in the office, in the factory or in the home some hours of service to aid the nursing of the sick in hospitals that have been depleted of nurses by the armed forces. Most of these nurse's aides learn their tasks in the lecture courses given by the Red Cross and in actual study at the bedside in eleemosynary and private hospitals. Many of them have had questions which they feared to ask or for which time was not available to answer. This handbook will help to meet some of the needs of those who want more information.

Nutrition in Health and Disease. By Lenna F. Cooper, B.S., M.A., M.H.E., Chief, Department of Nutrition, Montefiore Hospital, New York City, Edith M. Barber, B.S., M.S., and Helen S. Mitchell, B.A., Ph.D., Chief Nutritionist, Office of Foreign Relief and Rehabilitation Operations, State Department. Ninth edition. Cloth. Price, $3.50. Pp. 716, with 106 illustrations. Philadelphia, Montreal & London: J. B. Lippincott Company, 1943.

The ninth edition proves again the extent to which this work has earned for itself a place as a reliable textbook. The volume conforms closely to the curriculum guide for the schools of nursing published by the National League of Nursing Education. The changes consist of revisions to bring the material on vitamins, minerals and proteins up to date. New attention has been required for the discussions of the effects of cooking on nutrient qualities. All the food tables have been revised.

Burma Surgeon. By Gordon S. Seagrave, Lieut. Colonel, M. C., United States Army Forces in China, Burma, India. Cloth. Price, $3. Pp. 295, with 23 illustrations. New York: W. W. Norton & Company, Inc., 1943.

In the months that have elapsed since this book was offered to the American public it has become a nonfiction best seller well up on the list. The story of Dr. Seagrave's participation in the Burma conflict is told with humor and passion in a literary style that is convincing by the very directness of its approach to the subject. Between the time of the Japanese capture of the territory and the time of the writing of the book Dr. Seagrave lived intensely, and the book captures the excitement and strain of the period. The story of the development of nursing service utilizing the persons at hand indicates how many a physician in this period has met what seemed to be insurmountable difficulties.

Handbook for the Medical Secretary. By Miriam Bredow, Dean of Women, Eastern School for Physicians' Aides, New York. Cloth. Price, $2.25. Pp. 253, with 19 illustrations. New York & London: McGraw-Hill Book Company, Inc., 1943.

This is a comprehensive and practical textbook equally adaptable as a manual for classroom work or as a source of information for the medically inexperienced person who undertakes the specialized tasks of a doctor's office. The author's practical background in the field is revealed in every chapter. The subjects covered include personality, medical ethics, patients and their records, accounts, medicolegal matters, preparation of medical manuscripts, professional office procedures and medical terminology. The physician who directs the attention of his new assistant to this authoritative handbook will save himself much time and perhaps much trouble.

Textbook of the Ear, Nose, and Throat. By Francis L. Lederer, B.Sc., M.D., F.A.C.S., Professor and Head of Department of Laryngology, Rhinology and Otology, University of Illinois College of Medicine, Chicago, and Abraham R. Hollender, M.D., F.A.C.S., Assistant Professor of Laryngology, Rhinology and Otology, University of Illinois College of Medicine. Cloth. Price, $6. Pp. 595, with 170 illustrations. Philadelphia: F. A. Davis Company, 1942.

This volume is offered as a textbook for medical students who are limited in the number of hours available for the study of otorhinolaryngology. The volume is designed for easy reading. It is profusely illustrated with colored and black and white illustrations. Charts and tables tend to systematize the information that is offered. Simplified discussions of the anatomy and physiology of each of the parts precede technics of examination, pathology and discussions of individual disease conditions. The arrangement is by the regions involved. An excellent appendix provides a tabulation of the diagnostic and therapeutic facilities and approaches necessary for this specialty.

Nutrition and Physical Fitness. By L. Jean Bogert, Ph.D., Instructor in Experimental Medicine, Yale University, New Haven. Fourth edition. Cloth. Price, $3. Pp. 500, with 75 illustrations. Philadelphia & London: W. B. Saunders Company, 1943.

The fourth edition of this work indicates the popularity it has had from a large audience. So rapid is the progress of our knowledge of nutrition that even annual volumes fail to keep abreast of much that is new. The chapters on minerals and vitamins have been expanded from two to six chapters, five of which are entirely new. Tables of vitamin and mineral content of foods have been brought up to date. There has been much condensation in order to keep the book from growing beyond the limits of its purpose. It constitutes a most useful guide for the physician, dietitian and general reader.

Queries and Minor Notes

THE ANSWERS HERE PUBLISHED HAVE BEEN PREPARED BY COMPETENT AUTHORITIES. THEY DO NOT, HOWEVER, REPRESENT THE OPINIONS OF ANY OFFICIAL BODIES UNLESS SPECIFICALLY STATED IN THE REPLY. ANONYMOUS COMMUNICATIONS AND QUERIES ON POSTAL CARDS WILL NOT BE NOTICED. EVERY LETTER MUST CONTAIN THE WRITER'S NAME AND ADDRESS, BUT THESE WILL BE OMITTED ON REQUEST.

ACETYLCHOLINE AND PARALYSIS AGITANS

To the Editor:—A relative of mine has paralysis agitans. He has been treated with various medications without any definite relief. He was recently advised to take glutamic acid hydrochloride. Would you give me the latest information on such therapy. M.D., New York.

ANSWER.—As far as known there have been no reports on the use of glutamic acid hydrochloride in the specific treatment of paralysis agitans. A suggestion with regard to its possible value in this disease might be found in the recent work on the chemistry of the myoneural junction. Acetylcholine is intrinsically connected at the synapse with the potential of nerve action. The release and breakdown of acetylcholine are steps in a chain of reactions known as the "acetylcholine cycle" (Nachmansohn, D., and others: Action Potential and Enzyme Activity in the Electric Organ of Electrophorus Electricus: II. Phosphocreatine as Energy Source of the Action Potential, *J. Neurophysiol.* **6**:383 [Sept.-Nov.] 1943).

Acetylcholine is synthesized by the enzyme choline acetylase and broken down by another enzyme, choline esterase.

Some clinical observations suggest that *dl*-glutamic acid has a favorable effect on epileptic patients suffering from petit mal (Price, J. C.; Waelsch, Heinrich, and Putnam, T. J.: *dl*-Glutamic Acid Hydrochloride in the Treatment of Petit Mal and Psychomotor Seizures, THE JOURNAL, Aug. 21, 1943, p. 1153).

This action may be connected with the lowered rate of acetylcholine formation in petit mal. *l* (+)-glutamic acid appears to increase the rate of formation of acetylcholine about four or five times (Nachmansohn, D.; John, D. M., and Waelsch, Heinrich: Effect of Glutamic Acid on the Formation of Acetylcholine, *J. Biol. Chem.* **150**:485 [Oct.] 1943).

It is on this basis that the effects of treatment from the use of glutamic acid are to be at present evaluated.

It is not possible, however, to apply this information to a disease such as paralysis agitans except in a thoroughly empirical manner. There is no evidence that in paralysis agitans there is a decrease in the amount of acetylcholine at the myoneural junction or that a normal amount is broken down too rapidly. Glutamic acid hydrochloride is worthy of a trial in paralysis agitans under controlled conditions. The mental and physical alertness of the patient may increase, as was noted in the patients with petit mal treated by Price, Waelsch and Putnam. This action does not presumably occur at the myoneural junction but at the synapses within the central nervous system. In paralysis agitans, therefore, if any action takes place it may be central rather than peripheral.

EFFECTS OF MAGNESIUM FIRE BOMBS ON THE EYE

To the Editor:—I have been consulted about the effects of magnesium in the form used in incendiary bombs as it is apt to affect the eyes of workers. Bearing in mind that the application of moisture in extinguishing bombs seems to activate its burning properties, could you discuss the subject? Walter E. Constantine, M.D., Buffalo.

ANSWER.—Although there may be injurious constituents of incendiary bombs other than magnesium, the magnesium in these bombs is the same as that utilized in industry except as to particle size in some instances. In one form of that ocular operation known as cyclodialysis, a small plate of metallic magnesium is introduced between certain layers of eye tissues. This magnesium, evolving bubbles of hydrogen, tends to accomplish the objective of cyclodialysis. The accidental entry of magnesium spicules may lead to similar gas formations, and the extent of injury probably would be determined by the location. While magnesium foreign bodies on the surface of the eye would not produce any pockets of gas, the proteolytic action of this metal may make such a foreign body of greater consequence than that from some other metals, such as steel. Recent experience indicates that such is the case. Since magnesium is nonmagnetic and only slightly opaque to the x-rays, the location of foreign bodies of magnesium may prove difficult. For these reasons eye protection for workers in magnesium is highly desirable, and when eye injuries do occur prompt treatment is in order. The following references, although not directly related to the eye, may lead to more extensive information:

Tinozzi, F. P.: The Action of Some Light Metals and Their Alloys on the Tissues, *Med. sper., Arch. ital.* **8**: 129, 1941.
McCord, C. P.; Prendergast, J. J.; Meek, S. F., and Harrold, G. C.: Chemical Gas Gangrene from Metallic Magnesium, *Indust. Med.* **11**: 2 (Feb.) 1942.
Meek, S. F.; Prendergast, J. J.; Harrold, G. C., and McCord, C. P.: The Physiologic Action of Metallic Magnesium, *J. Indust. Hyg. & Toxicol.* **24**: 6 (June) 1942.
Schulz, R. Z., and Walter, C. W.: Magnesiogenous Pneumagranuloma, *ibid.* **24**: 6 (June) 1942.
Teleky, Ludwig: Injuries Resulting from Light Metal Splinters and Abrasions, *Indust. Bull.* **22**: 6 (June) 1943 (issued by the Industrial Commissioner of the State of New York).
Seelig, M. G.: A Study of Magnesium Wire as an Absorbable Suture and Ligature Material, *Arch. Surg.* **8**: 669 (March) 1924.

BARE LEGS AND UNCOVERED HEADS IN CHILDREN DURING COLD WEATHER

To the Editor:—The editor of our local newspaper has made inquiry concerning the effect of bare legs and hatless boys and girls during cold weather. Are there any studies which have ever been made on this subject? If so, will you be kind enough to give me reports to which I may refer? F. R. Nicholas Carter, M.D., South Bend, Ind.

To the Editor:—I have received the following in the mail from the South Bend *Tribune:* "Great interest is taken in the after-effects of the present custom of boys and young men not wearing hats and girls not wearing stockings in this cold weather. There is much speculation as to effect on their future health, perhaps years later. For the public's benefit please give the *Tribune* your opinion in a brief statement on possible results if this practice is continued. Should it cease? Will health be likely to be adversely affected and probably in what way?" I would appreciate an opinion about this. J. V. Cassady, M.D., South Bend, Ind.

ANSWER.—Controlled experiments on this subject seem to be lacking. Some years ago it was stylish for children to be bare legged and hatless in cold weather under the theory that it would harden them against colds. The effects did not substantiate this idea, and certainly most pediatricians are agreed that young children at least should be properly protected against unnecessary exposure of legs or heads in cold weather. There is some reason to believe that chilling of certain portions of the skin may effect a decrease in resistance to infection, at least in some persons. The scientific evidence for the exact relationship between such chilling and susceptibility to colds however is tenuous. Insult to the human body by allowing a completely unnecessary chilling does not seem like a practice which thoughtful physicians can recommend, although the fact that enormous numbers of people do expose themselves freely to cold suggests that this is harmful only infrequently.

POLIOMYELITIS AND LATE MUSCLE ATROPHY—LIFE EXPECTANCY AFTER POLIOMYELITIS

To the Editor:—Can you tell me what might cause an atrophy of muscles seemingly normal for fourteen years in a patient after an attack of poliomyelitis? Recovery during this period was sufficient so that he played on a college tennis team. For the past six months the calf muscles have dwindled in size until the legs are now about as large as the wrist. The young man walks around a great deal but has difficulty in pulling his legs forward as he walks. He recently married and seems happy. Any information you can give me on the later years in a victim of poliomyelitis will please me greatly—also any treatment. Can you tell me the length of life of patients who have had poliomyelitis? M.D., New York.

ANSWER.—It would appear that the present condition of the patient is not due to the after-effects of an old poliomyelitis but, rather, to some new injury to or disease of the muscle or its corresponding nerve. With normal recovery from poliomyelitis such atrophy would not occur after a period of fourteen years.

A person who has recovered from poliomyelitis, all other things being equal, can look forward to normal life expectancy.

STORAGE QUALITIES OF DRIED PLASMA

To the Editor:—For more than a year now through hot and cold weather we have been holding ten complete units of dried human blood plasma for emergency use in case of a disaster at this ordnance plant. Lacking adequate refrigeration facilities here we have merely stored the plasma in the general supply room, the temperature of which on a number of occasions last summer approached 100 F. Would this plasma have deteriorated to the extent that it would now be unsafe to use in cases of shock or the like? Thomas A. Neal, M.D., Carbondale, Ill.

ANSWER.—Properly dried human blood plasma withstands without deterioration low temperatures as well as temperatures well above those usually experienced during summer in this country. It is probable, therefore, that the dried plasma mentioned can be used not only for treatment of shock but for general use with perfect safety.